# Multiscale analysis of biological functions: the example of biofilms

**Annick LESNE**


Institut des Hautes Études Scientifiques
35, route de Chartres
91440 – Bures-sur-Yvette (France)

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Annick Lesne

*Institut des Hautes Études Scientifiques*
*Le Bois-Marie, 35 route de Chartres, 91440, Bures-sur-Yvette, France*
*& LPTMC UMR 7600, Université Pierre et Marie Curie-Paris 6*
*4 place Jussieu, F-75252 Paris Cedex 05, France.*

## 1 Introduction

Biological functions involve processes at different scales. This statement is obviously true for organismic processes like development. It is already relevant for a bacterial colony, the example on which we shall more specifically focus here. Understanding biological functions thus requires to *integrate knowledge and data* of different natures, available at different levels, and described within different frameworks, from quantum mechanics (for elementary intracellular processes e.g. light transduction) to stochastic kinetics to deterministic rate equations and continuous medium theory (e.g. elasticity theory or hydrodynamics). Beyond the epistemic issue of capturing a real process in descriptions and measurements prescribed by our own abilities and limitations, biological functions and their regulation present a greater challenge: they are *intrinsically and irreducibly multiscale processes*. Indeed regulation of a biological function has to bridge the overall state of the cells as well as some surroundings features with the basic ingredients and mechanisms at the atomic or molecular scale, in an adaptive and interrelated way. A bacterial cell itself has to perform a multiscale integration. Accordingly our analysis and modeling should follow the same line. For these two main reasons, multiscale approaches play an essential role in the way towards the integrated understanding of biological *functions*, and all the more of biological *systems*. We refer to [22] for a mathematical account and to [18] for another biological example.

We will first describe bottom-up approaches deriving the large-scale consequences of microscopic ingredients and their interactions; they rely on the notion of *effective parameters*. This notion is implemented in a systematic way in *homogenization methods*. It is also the basis of recursive integration methods developed to handle phenomena displaying long-range correlations, termed critical phenomena (Sec. 2). Choosing the proper model essentially depends on the investigated issue. In fact, each new question requires to devise the adapted model. We will mention the minimal models suitable for large-scale integration and the choice between deterministic or stochastic models (Sec. 3). We will detail a standard decoupling scheme exploiting scale separation to dissect a multiscale dynamics into more tractable lower-dimension problems (Sec. 4). We will then consider top-down approaches deriving the impact of macroscopic constraints on lower-level elements and mechanisms (Sec. 5). A brief comparison of multiscale issues currently encountered in physics and biology (Sec. 6) shows that it is of special importance in living systems to properly account for the feedback of collective features and emergent properties onto the underlying elements. In this aim, the means we favor are self-consistent methods, also well-suited to bridge partial knowledge at different scales (Sec. 7). Conclusion will enlarge the scope of the presented material (Sec. 8).

## 2 Bottom-up approaches: effective parameters

A first way for implementing a multiscale analysis is to travel across the scales in the bottom-up direction. This way is the standard one in physics and it has motivated much work, both technical

contributions (for instance the whole domain of statistical physics, see [5]) and epistemological account (see for instance [1, 31]). A basic notion is here that of *effective parameter*, encapsulating the net result of several mechanisms involving several degrees of freedom in a single quantity parameterizing at a higher level a structural feature, an interaction, or a contribution to an evolution law. Let us cite a few examples.

- *rate constants* involved in chemical kinetics are in fact not elementary (molecular) parameters: they are derived under simplifying assumptions from the stochastic (and possibly quantum) analysis of the reaction process. Within the general framework of Kramers theory, they are expressed as a function of the temperature and the free-energy barrier of the limiting step [11].

- in the case of chemical reactions involving several species and intermediate steps, some being possibly unknown, while we are interested only in the evolution of the concentration $a$ of one given substrate $A$, it is often fruitful to adopt a *pseudo-first-order* kinetic scheme: $da/dt = \sigma + ka$ [15]. Here the kinetic rates $\sigma$ and $k$ encapsulate in an effective way the influence of other species which we do not intend to describe explicitly. They will be fit in each experimental condition. Such a simplified scheme is valid only if the concentration of the marginal species can be considered as constant, either because they relax very fast to a stationary value (see Sec. 4), or because a regulatory circuit ensures their homeostasis. In a similar way, effective rate constants could be defined and computed to account for some structuration of the underlying medium [3].

- an *effective diffusion coefficient* can account on the average of microscopic inhomogeneities that are present within a porous substrate provided they have a finite characteristic size $a$. Introducing such a parameter allows to make use of a plain diffusion equation (that is, with a spatially constant diffusion coefficient and simple boundary conditions at the border of the inhomogeneous sample) at mesoscopic scales $dx \gg a$ [22, 29, 33].

It is to be strongly underlined that an effective parameter should have a restricted use: it makes sense only in the dimensionally reduced large-scale equation defining it. It does not necessarily share all the relationship and meanings of the corresponding bare parameter, despite sharing the same name. For instance, an effective diffusion coefficient does not necessarily satisfy the Einstein relation linking diffusion and friction coefficients.

Computing an effective diffusion coefficient is an instance of a more general method called *homogenization* [17, 33]. It is for example possible to replace a two-phase reactive medium with an effective homogeneous medium and to compute the associated kinetic rates and diffusion coefficient [3]. This approach has also been intensively developed in the context of porous media [33] and composite materials [26]. The physical motivation and intuitive justification has been supplemented with a rigorous mathematical analysis, specifying the validity conditions. In particular, it is essential to determine and validate what is the appropriate "representative volume". We here mean the size $dx$ of the regions of the initial system that can be considered as the elementary (infinitesimal) volumes of the homogenized system [4] and in which all the detailed microscopic structures and processes will be averaged. Roughly, $dx$ has to be large compared to the characteristic lengths of these microscopic structures and processes.

The notion of effective parameter is not limited to systems exhibiting a clear scale separation between microscopic fluctuations and macroscopic observables. On the contrary, it is often very fruitful to encapsulate in mesoscopic parameters the effect of long-range correlations between microscopic elements. Extending this idea in a systematic way, renormalization-group methods developed to handle critical phenomena (where long-range correlations propagate at all scales the influence of microscopic fluctuations) also rely on the notion of effective parameter, rather called *renormalized parameter* in this context. The essential properties of a critical system (i.e. a system with correlations at all scales and diverging correlation length) lie precisely in the relationship between bare and effective parameters; in other words, they lie in the transformation (the renormalization-group transformation) expressing how does the system modeling change when we change the scale of its description [5, 21]. We shall see in the following that biological systems,

mostly due to the presence of regulation and adaptation, escape a plain use of effective parameters and associated reduction to a purely macroscopic description, but yet effective parameters play a central role in self-consistent integrative approaches (Sec. 7).

# 3 What is the proper model?

A caveat is to be done right now about the term of "model" since it covers different notions and practices. We here endow it with a two-fold meaning: it first refers to the *theoretical framework* (e.g. quantum mechanics, partial differential equations, cellular automata, thermodynamics ...), then to the *representation* of the system and the mechanisms ruling its behavior within the considered framework (conservation laws, evolution laws, interactions ...). Several *models* might thus be associated to one and the same *system*. We claim that different models should be associated to the same system according to the investigated question. In particular, models entering a multiscale analysis should, in general, be designed on purpose so as to take into account inter-level couplings and allow integration (deriving the collective behavior of an assembly of elementary models and/or bridging different models designed at different scales).

## 3.1 Minimal models for integrative studies

Several multiscale issues require to determine the collective behavior of an assembly of sub-systems. In order to tackle this integration, we have to devise a *minimal model*, retaining among the richness of molecular details and processes only those controlling or participating to collective effects and having ultimately an observable impact at macroscopic scale. Other details could of course be essential in other issues, but they appear to be irrelevant degrees of freedom as regards emergent phenomena. A minimal model would be not only more efficient in large-scale numerical computations, but actually more relevant insofar as it yields more generic results. For instance, elementary units of the system can be modeled within a cellular-automata approach, involving a finite number of states for each unit, as well as discrete time and space variable with tunable units; the elementary level is thus described in a phase space of the lowest possible dimension, hence the most efficient for numerical simulations [30]. Conversely, the very existence of robust collective behavior supports the use of minimal model at microscopic scale, retaining only the details relevant to the dominant macroscopic features.

Minimal models, involving only the essential variables and parameters (possibly collective variables and effective parameters), are also to be recommended when we lack of knowledge on the wealth of microscopic ingredients and mechanisms. Indeed, compared to more detailed modeling, they avoid biases, over-interpretation and possible inconsistencies between the details that are accounted for and those that are ignored. They provide a *more faithful and more robust* modeling basis, because small changes in the microscopic ingredients will only slightly affect the value of the effective parameters without modifying the general form of the model. Minimal models are more relevant to bring out the main principles at work in the observed phenomenon, since they involve less arbitrary or tunable parameters, hence exhibit a greater statistical significance and discriminating power. This approach has been justified by Turing when he introduced, in its seminal paper on morphogenesis [34], a simple reaction-diffusion model exhibiting pattern formation in some suitable conditions.

## 3.2 Stochastic vs deterministic models

A large class of effective models is formed by *stochastic models*, whose evolution laws or the rules determining their state embed a probabilistic contribution. A first subclass is obtained by adding a noise term to the deterministic ordinary or partial differential equations describing the system evolution. These stochastic differential equations are currently called *Langevin equations*,

by extension of the equation of this kind introduced by Langevin [19] to account for Brownian motion. The noise term arises either from an ill-defined or variable external influence, either from the net result of microscopic degrees of freedom that we do not intend to take into account [20]. The latter description corresponds to a cutoff at high frequencies and short wavelength replacing the specific description of the "most microscopic" modes by an effective noise term. Stochastic calculus has been developed to handle such equation [12] but is full efficiency is limited to special kinds of noise terms (white or colored noises). Another subclass is formed by *stochastic processes*, whose evolution rules are essentially random, for instance a Markov chain whose dynamics is fully prescribed by the probabilities of transition between the instantaneous state and the following one [35]. In case of a Markov process, the characteristic times (correlation, relaxation and transition times of the process) are directly related to the eigenvalues of the transition matrix [13].

Modelers are confronted to the choice between deterministic and stochastic models. The essential point is that this choice is not bound to reflect the nature of the system, i.e. an intrinsic feature; rather, the model should fit the perception of the observers, their possible lack of knowledge or the question they intend to solve. The scale of the description and the scale at which predictions are to be done have a strong impact on this choice, for instance:
— statistical laws (e.g. the law of large numbers or central limit theorem) ensure that the macroscopic behavior of a stochastic microscopic model is deterministic;
— the macroscopic behavior of a deterministic but high-dimensional (or chaotic) microscopic model might be best captured within a statistical description.
These situations might be both encountered in modeling a given phenomenon. The paradigmatic example is diffusion, where a whole hierarchy of stochastic models can be introduced [23], at increasing scale and with an increasing number of simplifying assumptions (Markov, Gaussian, dimensionally reduced by projection): Liouville equation for the $N$-particle distribution function $f(\vec{r}_1, \vec{v}_1, \ldots, \vec{r}_N, \vec{v}_N, t)$, master equation for a discrete description in terms of the occupancy numbers of $q$ spatial cells, namely the evolution of the probability $P(N_1, \ldots, N_q, t)$, Smoluchowsky equation for the full one-particle distribution function $f(\vec{r}, \vec{v}, t)$, Fokker-Planck equation for the reduced distribution function $f(\vec{r}, t)$ or equivalently a Langevin equation with a white-noise term, or still equivalently a random walk. This hierarchy bridges two deterministic models and their parameters: at the microscopic scale the reversible description in terms of Newtonian dynamics, and at the macroscopic scale the irreversible diffusion equation [5].

### 3.3 The example of biofilms

A major functional specificity of biofilms is their multiscale organization: as regards the growth of the biofilm, its structural properties (density, porosity, thickness), its mechanical properties (attachment/detachment under the action of a flow), or its activity in consuming substrate (in applications to waste treatments), we have to describe and understand jointly the individual and global levels. Microscopic simulations can be developed in order to give an explicit basis to effective macroscopic models of biofilms and provide a framework to integrate experimental data. Two main types can be consdiered: cellular automata, describing the evolution of the particle contents of microscopic spatial cells according to some simple rules involving only the states of the neighboring cells, an individual-based model (IBM), describing the behavioral rules of each individual particle. Both can be used to integrate microscopic knowledge and determine the explicit expression of local effective rate constants, to be henceforth plugged in macroscopic models in terms of ordinary or partial differential equations. Confronting the predictions of microscopic and macroscopic models moreover specifies the validity conditions of a deterministic continuous approach, and conversely delineates the regimes (for the microscopic parameters or the macroscopic setting) where the effect of discreteness of the bacteria and stochasticity of their growth and attachment/detachment cannot be ignored. Such a bottom-up approach allows to take into account refined mechanisms or complicated geometry at the bacteria level and provide a framework to integrate experimental data obtained at different levels using different techniques.

# 4 Multiple-scale methods

Multiple-scale methods have been developed for more than a century to handle singular perturbation expansions, e.g. in celestial mechanics [5, 22]. The system is typically ruled by an evolution equation (ordinary or partial differential equations) depending on a dimensionless small parameter $\epsilon \ll 1$ in a singular way, insofar as the behavior of the solution for $\epsilon \to 0$ qualitatively differs from the behavior of the solution for $\epsilon = 0$. Let us consider for instance an ordinary differential equation where a multiplicative small parameter appears in front of a highest-order time derivative. The basic idea is to decouple "slow and fast variables" , that is, to exploit the scale separation (with scale factor $\epsilon$) for explicitly considering formally independent time evolutions. This strategy is called a *quasi-stationary approximation* because it amounts to first solve for the fast evolution while considering that the slow variables are frozen, then to plug in the asymptotic behavior of the fast variables (typically a stationary state) in the slow evolution equations. For instance, considering the coupled evolution

$$\left\{ \begin{array}{l} \epsilon dx/dt = f(x,Y) \\ dY/dt = g(x,Y) \end{array} \right. \tag{1}$$

we first solve the equation for $x$ at fixed value of $Y$. This yields the asymptotic value $X(Y)$ such that $f[X(Y),Y] \equiv 0$, that we plug into the evolution of $Y$. We thus obtain the slow evolution

$$dY/dt = g[X(Y),Y] \equiv G(Y) \tag{2}$$

for the slow ("macroscopic" ) variable $Y$. Note that neither $X(Y)$ nor $G(Y)$ depend on $\epsilon$: we here determine the behavior $\epsilon \to 0$ of the asymptotic regime of the solution of (1). This procedure can be made more obvious by a change $\tau = t/\epsilon$ of the time variable, yielding

$$\left\{ \begin{array}{l} dx/d\tau = f(x,Y) \\ dY/d\tau = \epsilon g(x,Y) \end{array} \right. \tag{3}$$

where setting $\epsilon = 0$ freezes $Y$ (it comes $Y(\tau) = Y(0) \equiv Y$ whatever $x$ is) and yields a close equation for $x$, parameterized by a constant $Y$, that determines the stationary state $X(Y)$ of the fast regime.

This approach is in particular encountered in the Michaelis-Menten analysis of enzyme catalysis $S \xrightarrow{E} P$ where $S$ is the substrate, $E$ the enzyme and $P$ the product [27]. The proposed kinetic scheme is the following:

$$S + E \underset{k'}{\overset{k}{\rightleftharpoons}} ES \xrightarrow{k_{cat}} P + E \tag{4}$$

Denoting

$$s = \frac{[S]}{[S]_0}, \quad c = \frac{[ES]}{[E]_0}, \quad p = [P], \quad \lambda = \frac{q}{k[S]_0}, \quad K = \frac{k'+q}{k[S]_0} \tag{5}$$

yields the system of coupled equations

$$\left\{ \begin{array}{ll} \epsilon\, \dot{c} = s - c(s+k) & c(0) = 0 \\ \dot{s} = -s + c(s+K-\lambda) & s(0) = 1 \end{array} \right. \tag{6}$$

It is exactly similar to (1) and the resolution strategy sketched above yields

$$V \equiv \frac{dp}{dt} = V_{max} \left( \frac{s}{K_{eq}+s} \right) \qquad V_{max} = k_{cat}\, e_0 \qquad K_{eq} = \frac{k'}{k} \tag{7}$$

In other situations, it is enough to reparameterize the evolution equation or make an appropriate change of variable to get rid of the singularity [28]. These methods, respectively of *strained*

*parameters* and *strained coordinates*, are reminiscent of the notion of effective parameters and they can be seen as an instance of renormalization [5].

More generally, scale-separation is a strong argument to eliminate fast variables, either by considering that they rapidly reach a stationary value, if any, else by averaging their oscillations. This is an instance of a more general philosophy intending to reduce the dimension of the complete description and extract a relevant macroscopic description, describing only a reduced set of macroscopic variables (in particular, variables varying only at macroscopic scales) [5, 14]. An often efficient clue is to consider the evolution of space or time average quantities, either the moments of the microscopic variables [6] or aggregated variables describing a coarse-grained version of the initial model [2, 13].

# 5 Top-down approaches: effective inputs

Another way of tackling multiscale approaches is to investigate top-down relationships, namely how macroscopic inputs, structures and constraints might affect the elementary processes and the features of the basic constitutive elements. Again effective quantities are useful to encapsulate in a low-dimensional expression (e.g. a field, a force, an energy landscape, a source term or boundary conditions) involving only a few parameters, a wealth of top-down influences. When external constraints arise via boundary conditions, it might be useful to "process" these conditions into local prescriptions at work inside the system; for instance, an external concentration (e.g. of oxygen) should be replaced after suitable computations involving assumptions on the intra-cellular medium diffusivity by an actual distribution inside the cell. As in more general contexts (see Subsec. 3.2), effective noise terms can be introduce to account for a variety of ill-identified external influences; e.g. an high-dimensional input that we do not want to describe in detail: what matters is only the resulting influence on the system at the chosen level of description

A purely physical but nevertheless inspiring example of top-down influences is fully developed turbulence, in which energy injected at a macroscopic scale $L$ cascades down to the microscopic scale $l_d$ at which viscous dissipation becomes efficient. In between, the energy transfer allows the development of nested eddies and other complex structures, exhibiting a statistical scaling behavior (e.g. the power spectrum follows a power-law dependence in the so-called inertial range $1/L < k < 1/l_d$. It has been proposed for capturing the essential scaling behavior and the long-distance universality (namely the insensitivity of the exponents with respect to details of the energy injection) to revert the bottom-up renormalization-group into a top-down *inverse renormalization-group*; namely, to integrate out the large-scale shells (or equivalently small-wave-vector cells), and to encapsulate their influence at lower scale (equivalently onto mode with a larger wave vector) into effective parameters [10].

Let us underline that an important advantage of effective descriptions, either bottom-up or top-down ones, is their parcimony, hence greater structural stability and significance: the resulting models involve only a few parameters and a few measurable variables. It is precisely because neither the microscopic details nor the macroscopic conditions are fully known, often not even all identified, that the models should involve only a coarse description, so as to avoid over-interpretation or spurious sensitivity of the results to the precise knowledge taken for granted in devising the model. This requirement of parcimony does not intend to mean that the biological reality is bound to be that simple, but that our description has to be unbiased and robust with respect to an additional detail or to the intrinsic variability observed between several identical biological systems, e.g. cells within a clonal population.

## 6 Basic classification: plain, critical and living systems

At this point, we can see an essential distinction in the multiscale logic of physical and biological systems, and accordingly in their respective multiscale analysis and modeling. In plain (mostly physical) systems, microscopic fluctuations average out and macroscopic observables can be identified with averaged quantities; they reduce to deterministic continuous fields that obey ordinary, partial or integro-differential equations with no mention of an underlying microscopic level. Standard examples are classical mechanics, hydrodynamics (Navier-Stokes equations) or chemical kinetics (mass action law). In striking but less frequently encountered *critical phenomena*, fluctuations are enhanced by long-range correlations and they persist at all scales up to macroscopic ones; they will qualitatively modify average behaviors, typically leading to anomalous laws. In biological systems, situation is yet different. Microscopic fluctuations are either *buffered by regulatory circuits* (even at relatively small scales where statistical laws not yet ensure an averaging out), either exploited and possibly amplified as a *source of variability* feeding selection-driven adaptation mechanisms. In the latter case, microscopic fluctuations potentially have repercussions at all scales while in the former case, discussed from the modeling viewpoint in the next section, they are controlled "from above" by means of feedback circuits that adapt the microscopic ingredients so as to get the proper macroscopic regime and ensure its maintenance.

This tripartite categorization has a parallel formulation in terms of number of degrees of freedom. In plain physical systems, *a few collective variables*, defined as averages over the microscopic degrees of freedom, are sufficient to describe the macroscopic behavior. Both critical systems and biological systems depart from this simple case by exhibiting *very many coupled degrees of freedom*. Averaging is no longer efficient to bring out the essential behavior. In case of critical systems, the efficient strategy is a recursive integration (renormalization-group methods) [5]. In biological systems, dimensional reduction will rather be achieved jointly at all scales in a *self-consistent way*, replacing at each level several degrees of freedom by a few effective terms; the observed robust achievement of the biological function provides a guideline to select the essential variables and to match the different levels together.

## 7 Circular causation and self-consistent approaches

A basic example of complex systems are assemblies of elements that modify their surroundings, enough to modify the features and behavior of the very elements, hence in turn changing the collective behavior of the assembly. Any such instance where collective features directly or indirectly affect their own element is termed *circular causality*. A physical macroscopic example is sand dune [16]; biological examples are ecosystems, bacterial colonies and possibly cell assemblies during cancerogenesis or development. We here encounter an instance of emergence, more precisely termed top-down causation [9]. In a word, self-organization and emergence are observed when bottom-up and top-down relationships are coupled, leading to co-evolution and adaptation.

We are thus led to the issue of bridging in a consistent way the bottom-up and top-down approaches to multiscale modeling. This kind of chick-and-egg problem can be properly formulated as *self-consistent equations*, expressing the identity of the macroscopic quantity $M$, influencing the state and properties $x$ of each element, and the collective quantity $\mathcal{M}_N[x_1(M), \ldots, x_N(M)]$ resulting from the conjunction of $N$ elements, in the limit[1] $N \to \infty$

$$M = \lim_{N\to\infty} \mathcal{M}_N[x_1(M), \ldots, x_N(M)] \tag{8}$$

It has thus the mathematical expression of a fixed-point equation

$$M = \Phi(M) \tag{9}$$

[1]This limit might induce important qualitative features and even generate serious difficulties; typically, the limiting quantity might be asingular function of $M$, e.g. exhibiting a transition between two smooth functions $\Phi_1(M)$ and $\Phi_2(M)$ in some value $M_c$.

In practice, the resolution of a fixed-point equation $M = \Phi(M)$ can be done recursively, given an initial value $M_0$ and computing $M_{n+1} = \Phi(M_n)$, provided the recursive scheme converges and the result does not depend sensitively of the choice of the starting value $M_0$.

An acknowledged example of self-consistent method is provided by *mean-field approaches*, in which the collective influence of microscopic elements on a given one can be expressed as a function of some quantity averages over all the elements (called an order parameter) and applies identically onto each element. Let us consider for the sake of simplicity the historical example of a spin system with pairwise interactions. The resulting influence on a given spin $\vec{s}$ of all its neighbors will be replaced by that of a mean field $h_{eff}(M) = aM$ depending on the average magnetization $M = \langle \vec{s} \rangle$. The spins $\vec{s}$ thus experience an external field $h_0$ and, instead of their pair-wise interaction, a mean field $h_{eff}(M)$; they henceforth can be formally considered as independent spins, whose average magnetization $M$ is given by a simple formula $M = B(h)$. Plugging in the field expression $h = h_0 + h_{eff}(M)$ yields a fixed-point equation $M = B(h_0 + aM)$, whose solution accounts in an average way of the spin pairwise interactions. Nevertheless, this approach is in general only an approximated one (local fluctuations are neglected), whose validity fails in case of long-range correlations generating relevant fluctuations at all scales; in such critical situations, more sophisticated renormalization-group approaches are to be developed [5, 21].

Self-consistent approaches extend beyond mean-field approximation. The general idea is to exploit the formal computation at a given scale of a quantity $M$ that also appears as a parameter tuning the basic ingredients on which the computation relies. Another related method, arising for instance in matched perturbation expansion, is to compute several macroscopic features all depending on an unknown effective parameter $X$ that is determined from a consistency condition between the computed feature, a global conservation law, or symmetry arguments. An example is provided by the topological constraints experienced by an elastic rod, for instance DNA molecules or elastic fiber, when its ends are anchored [24]. Its linking number $L_k$ is thus conserved and it is a feature of the molecualr assembly. The overall conformation of the rod determines its writhe $W_r$, and $L_k - W_r$ prescribes its total twist. Any local modification within the rod, e.g. a local structural change induced by some protein binding or by ions should be compensated so as to ensure the conservation of $L_k$. Top-down constraints here arise in the expression at microscopic scale of a global conservation law (conservation of a macroscopic quantity). Given the total linking number $L_k$, we might compute the writhe $W_r$ and the twist $T_w$, depending on some feature $M$ of the elastic rod, then write $L_k = W_r(M) + T_w(M)$ to determine $M$.

More generally, the presence of a global constraint (e.g. a fixed resource of a conservation law, as above) induces effective interactions between the elements. Such a global constraint might arise from the presence of a collective structure; it thus turns statistical correlations between the elements into effective couplings. It makes the whole behavior essentially non linear (even if the underlying microscopic dynamics is linear) with striking observable consequences like for instance a localization of the activity, in case of competitive effective interactions, or a synchronization, in case of positive interactions. It is indeed to underline that collective effects do not always reflect in large scale structures or behaviors: one possible consequence of a collective effect within an assembly of elements (particles, cells, individuals) could be the spontaneous emergence of very localized structures or events, typically resulting from non trivial correlations between microscopic fluctuations jointly with a positive feedback loop (self-activated reaction or any self-reinforcement mechanism) and a global constraint [25].

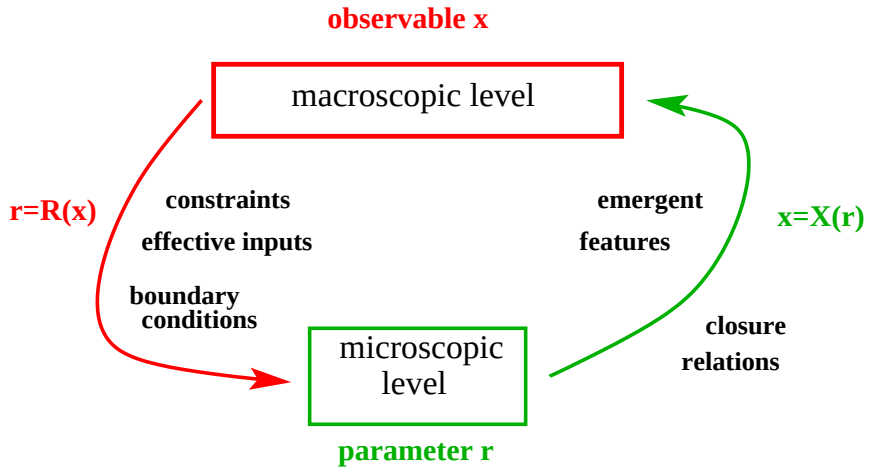


**Figure 1: Determination of causal loops with microscopic (individual-based models or cellular automata) and macroscopic (ordinary or partial differential equations) models of biofilms**

Let us illustrate this general analysis in the context of biofilms. A challenge comes from the fact that emergent properties of the bacterial population and the biofilm it produces might exert feedbacks on the very behavior of individuals. Accordingly, the modeling approach has to bridge a bottom-up description, in which emergent features are derived from a microscopic model, for instance an IBM simulation, with a top-down approach in which the global features are integrated as parameters controlling the IBM evolution. Equivalently, the focus could be put on an effective description at the macroscopic scale, in which standard differential equations describing the dynamics of the biofilm at the population level are fed with closure relations derived from the IBM study, itself constrained by macroscopic conditions (see Fig. 1). Obviously, we are faced to an instance of the above-mentioned circular causality in which individuals, their interactions and joint behavior modify their microenvironment which itself strongly constrains individual states and dynamics, in the spirit of multiscale simulations proposed in [7, 8]. We aim at deriving then solving self-consistent equations expressing the self-consistency of the multi-level organization and dynamics of the biofilm. The multiscale interplay of bacteria with the environment they generate can formally be described as follows (see Fig. 1). Population dynamics, with microscopic parameters $r$, modifies the environmental (macroscopic) features $x$, e.g. the temperature or nutrient concentration, according to a relationship $x = X(r)$ to be determined by means of IBM implementation. In turn, the state of the environment modifies the parameters $r$ of the dynamics (e.g. growth rate) according to a relationship $r = R(x)$, to be established from experimental observations. We then look of a consistent equilibrium state at the macroscopic level:

$$X[R(x)] = x \tag{10}$$

or, at the microscopic level:

$$R[X(r)] = r \tag{11}$$

Alternatively, we can rather focus on transient behavior and write recursive equations describing a slow adaptation of the biofilm at the macroscopic level:

$$x_{n+1} = X[R(x_n)] \tag{12}$$

or, at the microscopic level:

$$r_{n+1} = R[X(r_n)] \tag{13}$$

Such a multiscale approach should allow to account for remarkable behavior such as coexistence of species (whereas the macroscopic mean-field equations predict the persistence of a single species and exclusion of the other ones), functional differentiation, spatial segregation and other complex behaviors of the bacterial population.

# 8 Conclusion

The first aim of a multiscale analysis is to articulate experimental data and models available at different levels. It allows to bridge observations at different scales, to confront observations with mechanisms envisioned at another scale, and to integrate partial models into a consistent and explanatory account of the whole biological function or biological system under study.

An important preliminary step in multiscale analysis is to have recourse to minimal models, accounting at a given level only for the essential variables and parameters, that is, those having an impact at other scales and playing a significant role in the multiscale structure and dynamics [30]. Moreover, a minimal model is more sound on epistemological grounds when only a partial knowledge is available on the system. Indeed, it is important to avoid over-interpretation, for instance giving a role to some details while ignoring other details acting with an impact similar in strength and scope. Considering effective quantities (parameters, fields, inputs) has the same advantage, since it allows to encapsulate in tunable quantities a wealth of mechanisms without having to describe them explicitly nor even to have an exhaustive list. The use of effective models enlightens that the nature of the models should not be confused with the nature of the system. For instance, a statistical description is not necessarily associated to a random evolution low or spatial disorder. It can be chosen as the most efficient and economic way to account for the system features in case of a high-dimensional or chaotic underlying dynamics.

In all analyses, the structural stability of the results should be performed. It first covers an investigation of the significance of the results, whether they depend sensitively or not of a change in the model parameters or the accounting of an additional term. But beyond this quality assessment of the study, it meets a sensitivity analysis of the phenomenon itself, whether it requires or not finely tuned parameter values, and whether it is or not destroyed by the involvement an additional factor or interaction. In particular, it is meaningful to investigate the impact of statistical fluctuations (internal noise) on first model structural stability and, second, on processes themselves. Indeed, multiscale modeling often involves averaging quantities and thus raises the issue of the impact of statistical fluctuations on the resulting models and predicted behaviors. These statistical fluctuations, also termed *internal noise*, arise from the finite number $N$ of microscopic elements actually present in the system, causing a departure from the deterministic asymptotic behavior predicted by the limit theorems. The actual behavior is still random, as the relative fluctuations scale as $1/\sqrt{N}$ (unless some long-range correlations or other statistical pathology induces an anomalous scaling behavior). The issue is to determine whether this internal noise has a qualitative impact on the dominant behavior observed at macroscopic scale. A related issue is to investigate the functional impact of disorder, of compartmentalization, or of the intrinsic stochasticity of binding or chemical reactions.

The second aim is to unravel the multiscale logic of living systems; a main guideline is the inter-level consistency following from co-evolution, meaning that selection and ensuing adaptation occurred jointly at all levels of organization. What is striking in living systems and should be reflected in the multiscale analysis is the consistent multilevel organization with mutual influences between the different scales. Collective effects might have as a whole a feedback on the very properties of elementary ingredients, endowing them with new functionalities, that is a strong instance of emergence. This circular causality is typical in all complex systems and could even be taken as a definition of what is a complex system. Biological functions moreover rely on concerted evens at different scales, e.g. molecular events regulated at a macroscopic scale. Hence a multiscale approach is essential to capture the logical architecture of biological functions and regulation.

A practical guideline is the inter-level consistency and co-adaptation resulting from co-evolution under selection pressure. Accordingly, by contrast to plain physical systems[2], relevant multiscale analysis of biological systems makes use not only of effective parameters encapsulating at a given scale lower-level details (bottom-up reduction) but also of effective inputs encapsulating at the same scale the influences and constraints coming from super-structures at higher levels (top-down reduction) and write the self-consistency at the considered scale ( a scale that is possibly arbitrary or prescribed by the observation means).

We finally underline that the very notion and use of a model prevent from devising an "all-purposes" model that would allow to replace system study by questions addressed on the model. To be fruitful, a model should be specific to the investigated issue, ignoring details and degrees of freedom irrelevant *as regards to this question* and devised at the relevant scale (e.g. accounting for the available knowledge and experimental access. Similarly, a multiscale model should not intend to keep track of all details at all scales but only of the relevant details, whatever their scales, to unravel a biological function and regulation.

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