

# Multi-scale modelling in computational biomedicine

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## Abstract

The inherent complexity of biomedical systems is well recognized; they are multi-scale, multi-science systems, bridging a wide range of temporal and spatial scales. This article reviews the currently emerging field of multi-scale modelling in computational biomedicine. Many exciting multi-scale models exist or are under development. However, an underpinning multi-scale modelling methodology seems to be missing. We propose a direction that complements the classic dynamical systems approach and introduce two distinct case studies, transmission of resistance in human immunodeficiency virus spreading and in-stent restenosis in coronary artery disease.

**Keywords:** *computational biology; multi-scale modelling; molecular dynamics; cellular automata; complex networks*

## INTRODUCTION

Humans are complex systems: from a biological cell made of thousands of different molecules that work together, to billions of cells that build our tissue, organs and systems, to our society, 6 billion unique interacting individuals. Such complex systems are not made of identical and undistinguishable components: rather each gene in a cell, each cell in the immune system and each individual have their own characteristic behaviour and provide unique value and contributions to the systems in which they are constituents. Biological systems span many orders of magnitude through the scales in a continuous way, from the smallest microscopic scales up to the largest macroscopic ones. The sequence from the genome, proteome, metabolome, physiome to health comprises multi-scale, multi-science systems [1–3]. A pedagogical introduction to this concept and the field of multi-scale modelling in biology is provided by Schnell *et al.* [4].

In many cases, we can select an appropriate scale at which we wish to study a natural system. The history of science has shown how fruitful this approach has been. Such scale selection is a modelling decision (however, in a way, one may argue

that such scale selection is an emergent property of the system itself). In recent years the computational biology community has developed extremely powerful methods to model and simulate fundamental processes of a natural system on a multitude of separate scales, see e.g. [5,6]. The wealth of experimental data that has become available has made such *in silico* experimenting a viable methodology, which should allow for testing hypotheses and formulating predictions to be further tested in *in vitro* or *in vivo* studies [7]. Two recent special issues of the Philosophical Transactions of the Royal Society A, devoted to the Virtual Physiological Human, offer an impressive showcase of current state of the art in modelling and simulating organ systems [8,9]. However, the papers in those two special issues also clearly demonstrate the need to go beyond studying a single-scale, and in most papers approaches toward multi-scale modelling of human physiology are proposed. Indeed, the next challenge is to study not only fundamental processes on all these separate scales, but also their mutual coupling through the scales in the overall system, and the resulting emergent structure and function. Multi-scale biological systems display endless signatures

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of order, disorder, self-organization and self-annihilation. Understanding, quantifying and handling this complexity is one of the biggest scientific challenges of our time [10].

In this article, we provide a short review of multi-scale modelling in computational biomedicine. Next, we introduce a systematic approach to such multi-scale modelling, complementing the classic dynamical systems approach and its application to two disparate complex biomedical processes: transmission of resistance in human immunodeficiency virus (HIV) [11] and in-stent restenosis (ISR) [12].

Kitano identifies two distinct, mutually dependent scientific activities in computational biology: knowledge discovery through data—and text mining and modelling and simulation based analysis [7]. We mainly focus on the latter, but the inherent importance of the first will also be mentioned in the case of transmission resistance in HIV. As an aside one may ponder on the question how such thing as multi-scale data—or text mining could be realized, where one would specifically try to extract knowledge on the multi-scale aspects of a biological system and correlate data on different scales, in order to feed the now emerging multi-scale computational models (see e.g. [13, 14]).

In order to close the computational gap in Systems Biology, we need to construct, integrate and manage a plethora of models. A bottom-up data-driven approach will not work. Web and Grid services are needed to integrate often incompatible applications and tools for data acquisition, registration, storage, provenance, organization, analysis and presentation, thus bridging the integration gap. Even if we manage to solve the computational and integration challenges, we still need a system-level approach to share processes, data, information and knowledge across geographic and organizational boundaries within the context of distributed, multi-disciplinary and multi-organizational collaborative teams, or ‘virtual organizations’ as they are often called, thus closing the collaboration and interaction gap [15]. Finally, we need intuitive methods to streamline all these processes dynamically depending on their availability, reliability and the specific interests of the end-users. Such methods can be captured into ‘scientific workflows’ in which the flow of data and control from one step to another is expressed in a workflow language [15].

## MULTI-SCALE MODELLING

We live in four-dimensional space-time and multi-scale modelling usually refers to processes that act on widely separated spatial and/or temporal scales. Three-dimensional space is usually collapsed into a single spatial dimension, and biological systems range from the molecular scale ( $10^{-9}$  m) to the organism level (1 m) and from molecular interaction timescales ( $10^{-3}$  s) to a (human) lifespan ( $10^9$  s), therefore encompassing a  $10^9$  range in spatial scales and a  $10^{15}$  range in temporal scales [16]. However, as argued by Southern *et al.* [3], a more abstract scale separation in terms of *levels of biological organization* may be more natural to consider. They identify 10 different levels, from the quantum level, via the molecular, cellular, tissue, organ and organism-level to the environment, and for each level they review methods/models, ranging from e.g. molecular dynamics simulation of ion channels on the molecular scale, via continuous ordinary differential equations (ODEs) based models of e.g. cardiac cells on the cellular level, to stochastic compartmental models of severe acute respiratory syndrome outbreak on the environmental level. No matter how the scale separation is expressed, actual coupling between scales is at the heart of multi-scale modelling, and in computational biology ‘this kind of modelling is still at a very early stage’ [3]. This is not only true for computational biology. Despite the large body of literature on multi-scale models, there seems to be a lack of (formal) methodology and clearly specified strategies for multi-scale modelling [17]. However, some convincing ideas were recently published for biomolecular systems [18], that could be carried over to the field of computational biomedicine. Moreover, as Burrowes *et al.* [19] note: ‘Over the past several decades, our understanding of dynamic biological phenomena... has increased substantially. This has occurred over many scales of interest, but certainly not in a systematic manner, nor proportionately at each scale’. This will certainly have an impact on progress in multi-scale modelling, as it is of no use to link in scales on which no sufficient experimental data is available. As a consequence, to date there is hardly critical assessment available on the validity or accuracy of multi-scale models, nor critical comparisons of possible alternative multi-scale modelling strategies. As always, a strong integration of experimental work and computational modelling will be key to any progress in this field [7].

Yaliraki and Barahona [20] discuss some non-traditional ways to for multi-scale models for chemistry on the sub-cellular level, relying ‘on a series of coarse-graining directions which, starting from atomistic descriptions to using mechanical concepts, aim to show how the traditional chemistry of local interactions translates into global behaviours in biological systems’.

Burrage *et al.* [21,22] describe their approaches to multi-scale modelling for sub-cellular processes in the cell and on the cell membrane. Southern discusses in some detail the case of multi-scale modelling of ion channels [3] coupling simulations on the molecular scale, to obtain diffusion coefficients of potassium ions with Brownian dynamics simulations to obtain ion fluxes. In these examples the main assumption is that the time scales are separated, such that lower-level processes are much faster, implying that the lower-level processes are in quasi-equilibrium with the slower higher level processes and can be included at the higher level via e.g. constitutive equations or force fields. This type of multi-scale modelling, where microscopic processes (small spatial scales, fast dynamics) are coupled to macroscopic processes (large spatial scales, slow dynamics) has received most attention in the literature. However, as discussed in the next section, other types of multi-scale coupling also occur and should be investigated in more detail.

Another advanced example of multi-scale modelling is from Xu *et al.* [23] who propose a model for thrombus development. They couple a discrete Cellular Potts model of cellular behaviour to continuous models of blood flow and biochemical reactions. They assume that the growth of a thrombus is slow process, allowing a time splitting technique to be used where the transport equations are solved first, providing boundary conditions to the growth model. This is then iterated over many time steps of the slow model. This allows them to study in detail the growth of the thrombus, where initially activated platelets arrive at the front side of the thrombus, but as the thrombus grows, the flow fields change and activated platelets and blood cell clusters are pushed back and attached to the backside. This could explain inhomogeneity and later thrombus instability.

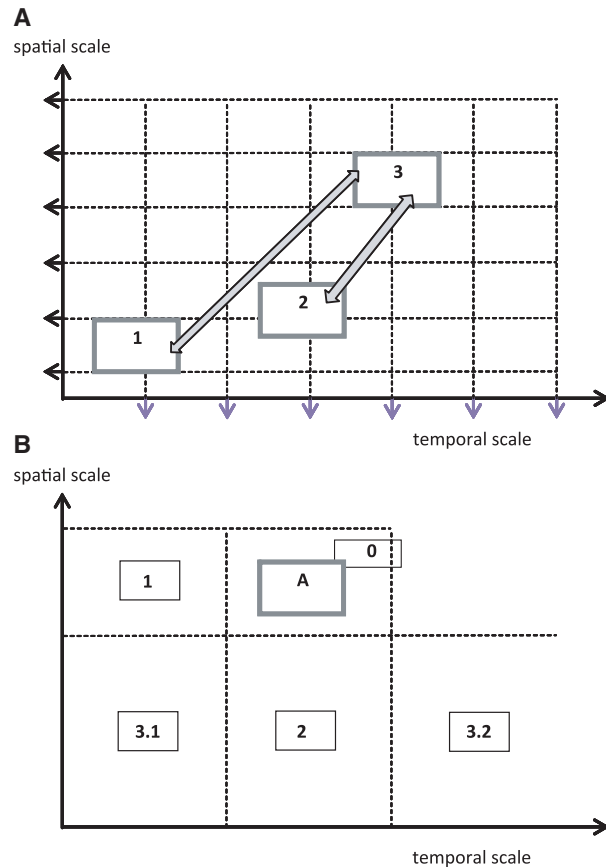
The most advanced multi-scale models and simulations in computational biology to date are those emerging from the IUPS Physiome project [16].

In this article, we can only scratch the surface of the Physiome related research and we will only mention a few highlights from the literature dealing specifically with multi-scale modelling. The Physiome aims at developing a standardized computational framework for human physiology. The main idea behind the multi-scale modelling in the physiome is ‘the application of continuum field concepts and constitutive laws, whose parameters are derived from separate, finer-scale models’, which is ‘the key to linking molecular systems biology (with its characterization of molecular processes and pathways) to larger-scale systems physiology (with its characterization of the integrated function of the body’s organ systems)’ [24]. This is again the micro-macro coupling as discussed earlier. Most advanced is the multi-scale model of the heart (see ref. [2,16] and also ref. [25] for deeper discussion on a multi-scale modelling paradigm to exploit temporal scale separation in systems of coupled ODEs). For other organ systems multi-scale models are on the drawing table, and with the current wave of projects in e.g. the Virtual Physiological Human initiative (see [http://ec.europa.eu/information\\_society/activities/health/research/fp7vph/index\\_en.htm](http://ec.europa.eu/information_society/activities/health/research/fp7vph/index_en.htm)), one may expect to see rapid progress. For instance, in case of the pulmonary system, detailed models on the organ level (anatomically based models of the lung, airway and vascular trees), the tissue level (tissue mechanics, microcirculatory flow) and cell levels (erythrocyte gas kinetics) are available [19] but their integration into a multi-scale model for a virtual lung is only beginning to appear in the literature [19,26]. Another challenging organ system is the musculoskeletal system. The case of multi-scale modelling of the human femur is discussed in ref. [27], again demonstrating that on many levels detailed models are available, and that linking them together through the scales is where the current challenge lies. Interestingly, this article nicely demonstrates the ‘middle out’ approach (as opposed to bottom-up or top-down), where one picks the biological level of interest as the starting point, and then works up and down the scales as required [28]. The interesting event is the fracture of the femur (the organ level), which also depends on higher levels (the body level, providing bone loading conditions) and lower levels (tissue level, to provide constitutive equations and failure criteria; cellular level to be able to account for bone remodelling) [27].

## A MULTI-SCALE MODELLING STRATEGY

Despite the widely acknowledged need for multi-scale modelling and simulation, there is a scarcity of underpinning literature on the methodology and generic description of the process. There are many excellent papers that present multi-scale models (as discussed above), and some specialized journals exist (e.g. *Multi-scale Modelling and Simulation*, *International Journal on Multi-scale Computational Engineering*), but few methodological papers on multi-scale modelling have appeared so far (some examples are [29, 30]). The Complex Automata Simulation Technique (COAST) Project (<http://www.complexautomata.org>) aims to help filling this gap by developing a multi-scale, multi-science framework, coined complex automata (CxA), for modelling and simulation of complex systems, based on a hierarchical aggregation of single scale models, which are assumed to be Cellular Automata [31]. Note, however, that the methodology is not restricted to Cellular Automata, but also includes agent based models [32], and is easily generalized to other modelling paradigms. The CxA methodology is described in detail in ref. [17] and references therein. Here we will shortly review the main ingredients. Please note that in further description of our strategy there are a few issues at stake: (i) how to identify the single scale processes; (ii) how to model the single scale processes; (iii) how to couple them between the scales. In this manuscript we do not discuss the details of the single scale models (some of them were mentioned in the previous section), nor their limitations, but we assume that a well-validated single scale model is available.

First, a system is decomposed into its subsystems for which the characteristic scales are identified. So, typical temporal scales could be based on e.g. the inverse of reaction rates, diffusion time over a characteristic spatial scale, or the duration of a cell cycle. Spatial scales could reflect e.g. the levels of biological organization as mentioned above, but could also allude to typical spatial dimensions over which a chemical agent diffuses, or other geometric characterizations. A Scale Separation Map (SSM) is then created, where the temporal scale is plotted on the horizontal axis and the spatial scale on the vertical axis and each subsystem is plotted as a rectangle (note that the size of the rectangle has a clear meaning in the CxA theory). Next, the coupling between subsystems is drawn as directed edges between the boxes.



**Figure 1:** Scale separation diagrams. **(A)** Scale map showing three subsystems and an example of mutual couplings. **(B)** Interaction regions on the scale map.

The SSM is therefore a graphical representation of all single-scale subsystems that make up the full multi-scale system in terms of their spatial and temporal scales, and in terms of their mutual coupling. Figure 1A shows an example of an SSM, in which three subsystems have been identified. Subsystem 1 operates on small spatial scales, and short temporal scales, subsystem 2 at intermediate scales and subsystem 3 at large scales. This could represent processes operating at the micro-, meso- and macro-scales, for example.

By considering two mutually coupled processes on the SSM, five interaction regions are identified, each giving rise to specific multi-scale coupling paradigms. Consider two processes, A and B, each with their own spatial and temporal scales. Assume that A has the largest spatial scale. We can now investigate the different possibilities of placing B on the map relative to A. This leads to a classification of interaction regions, as shown in Figure 1B. Depending on the location of B, we can identify

the following five interaction regions (note that we do not have to consider other regions of the scale map, because the roles of A and B are simply reversed, and we revert to one of the cases identified below):

Region 0: A and B overlap, and there is no scale separation;

Region 1: A separation of temporal scales at the same spatial scale;

Region 2: A separation in spatial scales like coarse and fine structures on the same temporal scale;

Region 3: Separation in both temporal and spatial scales.

If B is located in region 3.1, this leads to the classical situation of micro  $\Leftrightarrow$  macro coupling, with a fast process occurring on a small spatial scale coupled to a slow process occurring on a large spatial scale. This type of multi-scale model has received most attention in the literature, and the coupling paradigms explained earlier have mostly been applied in this region. Note that the approach taken by the Physiome project where lower level models provide constitutive equations to higher-level models also fall in this interaction region. When B is in region 3.2, we have the reverse situation: a slow process acting on a small spatial scale is coupled to a fast process acting on a large spatial scale. We believe that this is very relevant to the coupling of biological with physical processes, where a biological process, such as the slow response of cells, is coupled to a faster physical process on a larger scale (e.g. endothelial cell in arteries reacting to the cyclic blood flow).

Note that, it may not always be possible to have a clear scale separation. In such case one would hope that models with some form of hierarchy could be applied (think of e.g. local mesh refinement in fluid flow solvers). In terms of the SSM, this would result in a hierarchy of overlapping spatio-temporal scales.

The concept of the SSM is applicable to many complex systems, for example, coral growth [33] or thrombosis and snow transport/deposition [34]. Indeed, Evans *et al.* report on a SSM for ISR [12] (see also Case 2, below), Lawford *et al.* report on a SSM for the response of the native endothelium to shear stress [35] and Fazekas *et al.* [36] used diagrams that are close to a SSM in multi-scale

modelling and time-scale analysis of the human limb. Moreover, we are aware of ongoing activities where SSMs have been set up for the urothelium and for ovum transport and implantation (P. Lawford, personal communication). The SSM by itself is a qualitative modelling tool, as it helps to disentangle and organize the often large amount of relevant processes at stake, as e.g. in the case of ISR [12]. However, the SSM is just a starting point of the CxA methodology. The next paragraphs introduce two other important principles, that of the *domain*, and of *coupling templates*.

Besides the interaction region, another important characteristic of multi-scale coupling is that of the domain. We identify single-domain (sD) coupling when processes A and B act on the same domain and multi-domain (mD) coupling when processes A and B act on separate domain that are coupled via a boundary or small overlap region. The micro  $\Leftrightarrow$  macro coupling in interaction region 3.1 usually is of sD type. A nice example of interaction region 3.2 would be endothelial cells in arteries in contact with and reacting to oscillatory shear stress due to oscillating blood flow, which is clearly an example of mD coupling. In ref. [17], we provide many more examples.

Another level of detail is to consider *interaction templates*, where the actual coupling for each of the interaction regions and for sD and mD cases for specific types of single scale models are specified. This is a new concept that opens up on the one hand a way to investigate mathematical issues related to scale separation errors [37], and on the other hand provides the basis for generic multi-scale simulation environments. For further details on CxA we refer to [17, 38].

We should point out that very few environments exist that can handle the coordination of coupled models whose component modules may be expressed using different formalisms (ODE/PDE, FEM, cellular automata, agent-based models, other discrete approaches). This issue has been addressed by Zeigler *et al.* [39]. We developed Multi-scale Simulation Library and Environment (MUSCLE), a multi-scale simulation environment that allows to implement multi-scale scale models that are expressed as a CxA, and allows coupling cellular automata and agent-based models [40]. Another example of such environment is the Model Coupling Toolkit, which is designed to couple

large scale parallel models together [41]. Hetherington *et al.* [42] discuss what they call ‘the challenges of multi-scale model management in systems biology’ and introduce XML based services for model integration, as well as for storing of model parameters and results, and for storing and analysis of the models themselves. They also review a number of modelling frameworks relevant to multi-scale simulations.

To summarize, the SSM itself is a graphical description of complex multi-scale models. The arrows on the graph have real meaning and this is where the real multi-scale modelling is found. The notion of interaction regions and coupling templates could guide the way in methods for actual scale coupling. However, in the end, it is the details of the application that dictate how this should be done.

### CASE 1: TRANSMISSION OF RESISTANCE IN HIV

During the past 10 years significant progress has been made in the treatment of viral disease infected patients. For instance, around 20 antiretroviral drugs are now available for treatment of HIV with patients taking a combination of usually three drugs from at least two different classes of antiretroviral drugs in order to achieve complete suppression of the virus [43].

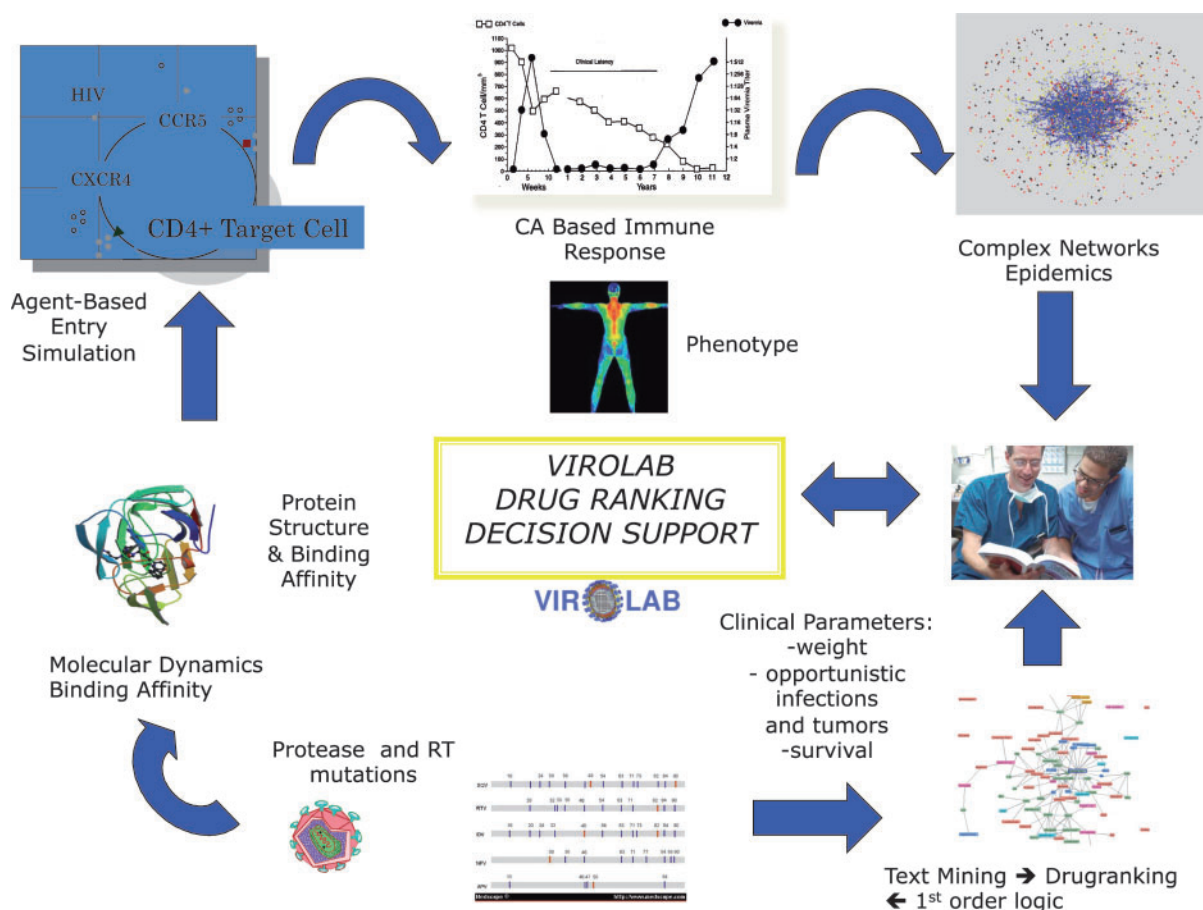
In a considerable proportion of patients, however, complete suppression of viral replication is not reached, resulting in the rapid selection of drug-resistant viruses and loss of drug effectiveness. Resistance can be achieved by a multitude of combinations of mutations, and frequent cross-resistance exists between drugs from the same class, complicating the clinician’s decision process. Such a decision process requires translating information on virus mutations to *in vitro* changes in drug sensitivity or to *in vivo* clinical responses to specific regimens.

ViroLab (<http://www.virolab.org/>) [44–46] was developed to give medical doctors a decision support system to rank drugs targeted at patients and to provide virologists an advanced environment to study trends on an individual, population and epidemiological level. Virolab is a multi-scale modelling, simulation and datamining environment for infectious diseases, going from molecule to man and back, see Figure 2.

Statistical and immunological models are needed to study the dynamics of the HIV populations and molecular dynamics models to study drug affinities, in addition to rule-based and parameter-based decision support. We added cellular automata (CA) and molecular dynamics modelling of HIV infection and AIDS onset. All these models operate on a large range of length and time scales as sketched in the SSM in Figure 3. The single-scale models appearing here will be shortly discussed.

A mesoscopic model to study the evolution of HIV infection and the onset of AIDS is used that takes into account the global features of the immune response to any pathogen, the fast mutation rate of the HIV, and a fair amount of spatial localization, which may occur in the lymph nodes. ODE (or partial differential equation) models are insufficient for describing the two extreme time scales involved in HIV infection (days and decades), as well as the implicit spatial heterogeneity. Non-uniform Cellular Automata models were developed to study the dynamics of drug therapy of HIV infection, which simulates four-phases (acute, chronic, drug treatment response and onset of AIDS). The model for prediction of the temporal behavior of the immune system to drug therapy qualitatively corresponds to clinical data [47]. The influence of patient specific mutations on the drug binding affinities can be calculated through high performance Molecular Dynamics Simulation. In a recent article results were discussed for the prediction of binding free energies for Saquinavir-bound HIV-1 Proteases [48].

The bio-statistical analysis of the HIV-1 genotype datasets aims to identify patterns of mutations (or naturally occurring polymorphisms) associated with resistance to antiviral drugs and to predict the degree of in-vitro or in-vivo sensitivity to available drugs from an HIV-1 genetic sequence. The statistical challenges in doing such analyses arise from the high dimensionality of these data [49]. Direct application of the well-known mathematical approaches to analysis of HIV-1 genotype results in a lot of problems. The problem stems from the fact that in HIV DNA analysis, the main scope of interest is the so-called relevant mutations [50], a set of mutations associated specifically with the drug resistance. These mutations might exist in different positions over the amino-acid chains. Moreover, the sheer complexity of the disease and data require

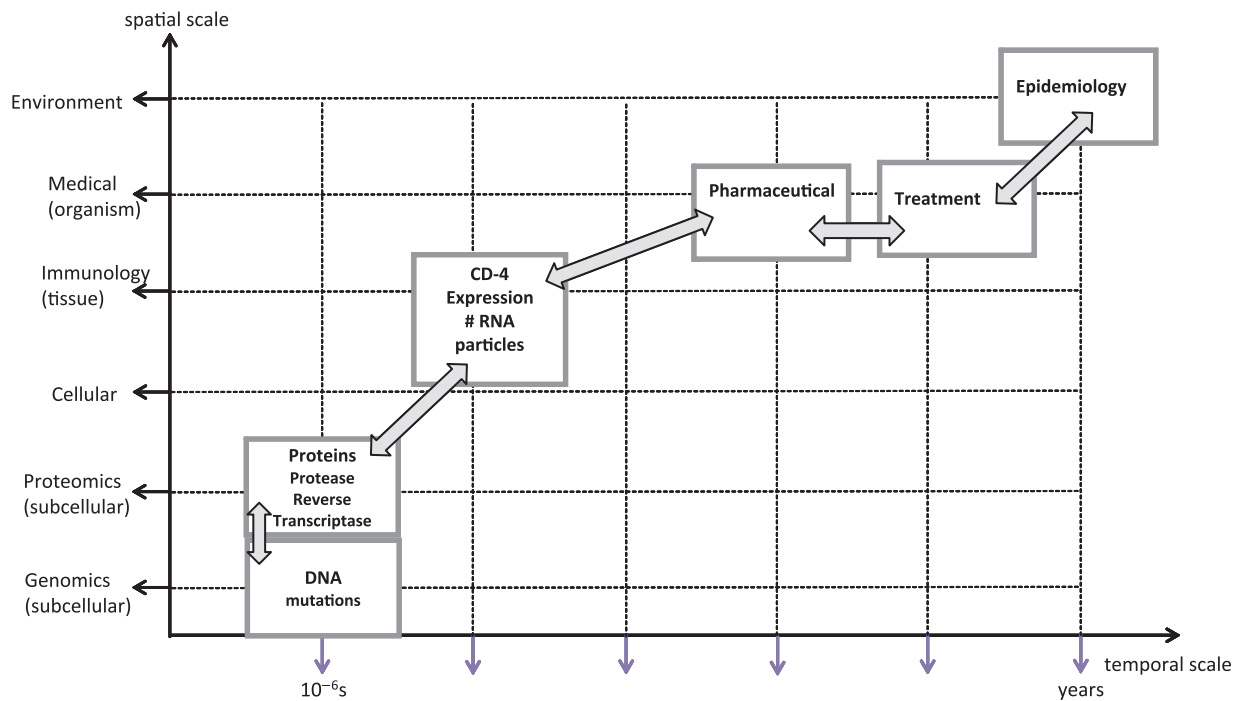


**Figure 2:** The ViroLab Framework with its components. From the bottom going left-up: patient specific viral load, mutations and  $CD^{4+}$  information is used by the Molecular Dynamics calculations to estimate the binding affinity of various drugs with Reverse Transcriptase and Protease. The binding affinities as well as the mutations are used to estimate the entry of the virus into the cell. Next the binding affinity, entry process and  $CD^{4+}$  count and viral load are used to estimate the immune response, finally the immune response and the binding affinity are used in modelling the individual nodes in a complex sexual interaction network. From the bottom to right-up: context-sensitive text mining distills relations between drugs and mutations and presents these as ranking rules. The decision support kernel integrates both types of information (simulation and text mining) into integrated decision support for drug ranking.

the development of the reliable statistical technique for its analysis and modelling. A possible approach is through Bayesian Network Learning [51, 52], a datamining technique allowing graphical mapping of conditional dependencies in genetic sequences. Such a technique could take into account epistatic interactions between mutations from which an *in silico* model can be built, representing the *in vivo* fitness of the virus under drug selective pressure [53].

The infection spreading is modelled as a stochastic process taking place over a sociological sexual network. Key ideas like network structure, network generation, and node dynamics are applied. The

models are validated against real historical data. The model has some distinctive features: it takes into consideration all the existing kinds of HIV spreading. Homosexual and heterosexual spreading is described by a scale-free network, drug users spreading is described with the assumption of homogeneous mixing inside the exposure group. All the network parameters have been taken from the medical literature and were fixed during the numerical experiments. The experiments show a promising correspondence between the model results and real demographic historical epidemiological data [11]. This model may be used as a ‘back-calculation’



**Figure 3:** An SSM for the case of transmission of resistance in HIV.

[54] model and as a predictive model, because the complex network technique mimics the underlying mechanism of HIV transmission.

## CASE 2: ISR

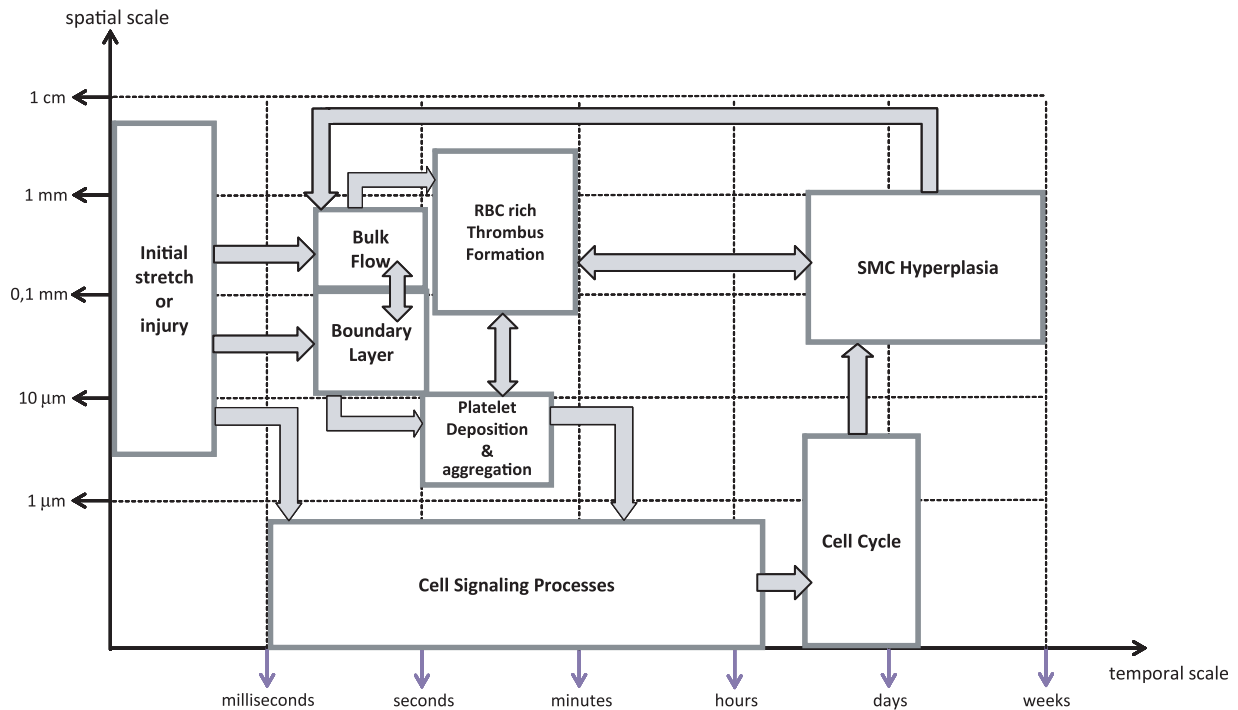
Coronary artery disease refers to the accumulation of atheromatous plaque within the wall of the coronary arteries and remains the most common cause of death in Europe. Percutaneous coronary intervention is a possible treatment strategy where an inflatable balloon is used to reopen the stenosed artery. A metal frame (stent) may also be deployed to provide a scaffold to maintain an open vessel lumen. Unfortunately, restenosis, i.e. a return of the vessel lumen to a size similar to that before intervention, remains a significant complication. This ISR is largely a result of vascular smooth muscle cell (SMC) proliferation. ISR remains an increasing and significant problem, given the ageing nature of the population. Modelling ISR should aid in understanding of this complex pathophysiology, and strategies to prevent it, and requires coupling biological processes acting on the micron scale up to hemodynamic processes acting on the centimetre scale (hydrodynamics, advection–reaction–diffusion, fluid–structure interaction, particle transport in

boundary layers, tissue growth and single cell response). These processes also involve widely separated time scales, from seconds to months.

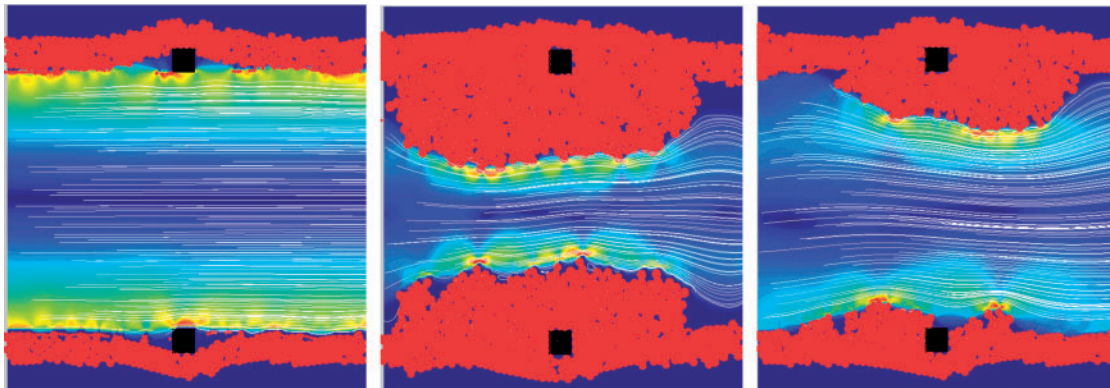
The key single scale processes involved in ISR are (for details, see ref. [12] and references therein) initial arterial injury due to stent deployment (including details of geometry of stent); platelet deposition and aggregation; RBC rich thrombus formation; SMC hyperplasia; Cell signalling and the Cell Cycle; SMC hyperplasia; vessel remodelling; cyclic flow, shear, and strain; and in case of drug eluting stents transmural diffusion and advection. After a detailed study of all these relevant processes Evans et al. proposed SSM for ISR [12], and Figure 4 reproduces a simplified version (without the drug elution and vessel remodelling).

Currently all single-scale models have been developed and are being integrated into a coupled multi-scale simulation using the COAST coupling libraries [40]. Figure 5 shows an example of a two-dimensional version of the model, showing the initial conditions after stent deployment, as well as the resulting restenosis for bare metal stents and drug eluting stents [55]. The inhibitory effect of the drugs on the restenosis is clearly visible. Currently we are working on validating these simulations against detailed experimental data.





**Figure 4:** Simplified version of the SSM for ISR showing the minimum number of explicitly modelled processes considered necessary for the system model to remain representative.



**Figure 5:** Two-dimensional benchmark geometry (left), sketching a vessel of length 1.55 mm, width 1 mm, where two square struts of side  $90 \mu\text{m}$  have been deployed into the cellular tissue. SMCs are depicted as circles with (mean) radius of  $15 \mu\text{m}$ . Resulting restenosis after 16 days, with a bare metal stent (middle) and a drug eluting stent (right).

### Key Points

- Biological and biomedical systems are multi-scale, multi-science systems and this multi-scale nature needs to be addressed in order to fully understand their seemingly endless complexity.
- The amount of multi-scale models appearing in the literature is slowly increasing, but a critical evaluation and comparison of alternative multi-scale modelling strategies, including their validation, is not yet available.
- The COAST and VIROLAB projects propose conceptual methods for multi-scale modelling in computational biology and demonstrated their use for modelling ISR in coronary artery disease and in modelling transmission of resistance in HIV.

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