An agent-based model of microRNA-mediated gene regulation: simulation and interpretation of observational data

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Motivation

Gene regulatory networks, especially those involving non-coding RNA, represent the paradigm of complex systems: many simple processes, under selective pressures, synergistically interact to produce a desired global behaviour, often exhibiting hierarchical self-organization. The mathematical modelling of this kind of systems by differential equations is an hard task, mainly because the great number of required reaction parameters, for which reliable values are rarely available. Agent-based models, allowing us to abstract from biochemical detail, are an useful tool to investigate gene regulatory mechanisms. Moreover, the agent approach provides models that are inherently multi-scale and stochastic, addressing two main problems of Systems Biology. In this work we report about an agent based-model developed to interpret a set of observational data, simulating some different scenarios on the basis of available biological knowledge.

Methods

MicroRNAs are short single-stranded RNA molecules that negatively regulate gene expression at post-transcriptional level. In the Cell Biology Laboratory, we depleted by decoy transfection - two microRNAs (miRNA 221 and 222) in Human Umbilical Vein Endothelial Cells. Correspondently, we found an important change in the overall microRNA signature not in the depleted microRNAs only- and in the expression of a housekeeping gene, c-kit, that is under the post-transcriptional control of miRNA 221 and 222. The c-kit expression showed a marked oscillatory pattern that vanished with time, notably reaching lower values after microRNAs depletion. This kind of behaviour is the hallmark of a regulation feedback, whose aim is to maintain stable the number of c-kit molecules inside the perturbed cell. The regulation is consistent with several molecular pathways depicted by three distinct scenarios: 1. the auto-regulation of c-kit by a negative feedback loop, 2. the auto-regulation of the microRNA network by a negative feedback loop, and 3. a combination of both the feedback loops. The three scenarios were simulated by an agent-based model of the system. The model was developed using the NetLogo 3.1.4 platform, with a decentralized swarm approach and multiple agents locally interacting in agreement with simple rules, dictated by biological knowledge. To account for the cooperative and aspecific action of microRNAs, another coding gene under microRNAs control, besides c-kit, was considered.
The cell, in a simplified 2-dimensional representation, was divided in nucleus and cytoplasm. Agents were created to represent a microRNA network constituted by miRNA 221, miRNA 222 and other 50 microRNAs, that regulated c-kit and the other coding gene in the model, gene alfa, but were not depleted by decoy transfection. Other agents were created to represent c-kit mRNA, c-kit protein, gene alfa mRNA, gene alfa protein, ribosomes, decoy molecules, transcription factors of microRNAs and coding genes, promoter regions of microRNAs and coding genes. To model the negative feedback loops, we allowed proteins and microRNAs to occupy, for a limited amount of time, their promoters, preventing the attachment and firing action of the transcription factors. Agents moved randomly inside the cell and received a stochastic life-time.

Results

The simulations clearly showed the plausibility of a microRNA post-trascriptional regulation network, auto-regulated by a negative feedback and synergistically interacting with the coding gene transcriptional regulation. The observed time-varying expression of c-kit was interpreted as a macro-behaviour emergent from micro-causes.
In our experience, agent-based modelling makes the inherent complexity of the multiple, interacting processes of gene regulation manageable, by choosing an appropriate level of abstraction. Moreover, the behaviour rules, that constitute the backbone of the agent-based model, are made of the same natural language narratives commonly used by biologists to explain phenomena, greatly strengthening the interdisciplinary nature of the research. In our opinion, abstraction and interdisciplinariety makes the agent-based modelling approach suitable to address the question about the interplay between molecular pathways in gene regulatory networks.

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