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'Does the 'Genome' Throw Dice Then? About Individualized Medicine, Einstein and Bohr

Abstract:
Some 90 years ago, Physics was in crisis, at least as felt by Einstein. The fundamental uncertainty proclaimed by Heisenberg and Born, and embraced by Bohr, was unacceptable to the former, as was the corresponding departure of causality. Today, medicine is in a comparable crisis, ill-realized as such, but still: That an accepted medicinal drug works on a large population may be certain, but whether it cures any individual is not. We shall claim that through individualized medicine, Einstein should be right in this instance: by acquiring additional information about the individual's genome and state, therapies should become robust.

This increased certainty seems to be compromised again in tamoxifen-treated breast cancer, where drug resistance arises. Outcome is again uncertain, now for up to 50%. The standard explication is genetic heterogeneity of the tumor, with some cells having been mutated so as to overexpress resistance factors. This will return us to the possibility that acquiring additional information, now on the tumor, for instance by single cell genomics, should remove the uncertainty.

But then there is the issue that even clonal cells can be heterogeneous in their phenotype. We will show how an epigenetic transcription-clock mechanism may lead to transcription bursting and to substantial noise in mRNA and perhaps protein levels. But how and when is this 'noise' 'special', i.e. different from random noise that is default to all molecular systems? We will discuss how the Fano factor (ratio of variance to mean) reflects the special nature of this noise. This special nature may produce behavior not expected for the average cell, which is amplified by selection. If dynamics is slow enough, the corresponding cell-cell heterogeneity may increase drug resistance of the cell population. We shall show how an integration of precise experimentation, molecular tinkering, mathematical modelling and analysis, may enable us to understand or even revert de-regulated behaviour of biological systems. But whether this will prevent the genome from throwing dice is still an open question.

About:
Hans Westerhoff is a long time researcher of how dynamic interactions between components of biological systems generate function. After a PhD at the University of Amsterdam and stays at the University of Padova, the US National Institute of Health and the Netherlands Cancer Institute, he is now Professor of Synthetic Systems Biology at the University of Amsterdam, emeritus Professor of Systems Biology at the University of Manchester, and Professor of Microbial Physiology at the VU University Amsterdam. He is one of the drivers of the silicon human initiative and the Infrastructure for Systems Biology Europe (ISBE).