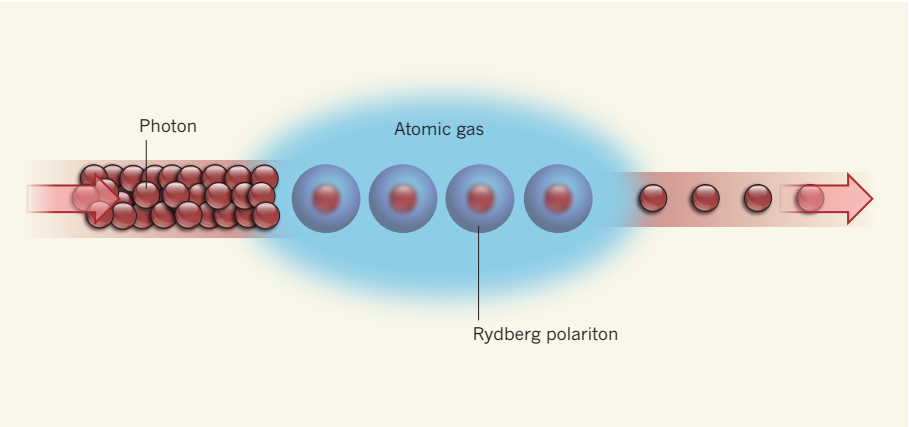

Figure 1 | A stream of single photons. Peyronel *et al.*[2] have directed a beam of overlapping photons into an atomic gas in which single photons are converted into collective excitations known as Rydberg polaritons. The polaritons, which can be thought of as spheres comprising many atoms and one photon, strongly absorb additional photons. On exiting the gas, the polaritons are converted back to individual, non-overlapping photons.

principal quantum number n (a Rydberg state[5]), the EIT condition can be easily violated by weak interactions between the atoms. For an n of about 100, a single Rydberg atom will cause a violation of the EIT condition for all other atoms within a 'blockade radius' of 10 micrometres. This Rydberg blockade produces record nonlinearities, as shown recently by Adams and colleagues[6], and has been used to entangle neutral atoms separated by micrometre-scale distances[7,8]. A Rydberg polariton can be thought of as a 10-μm sphere containing many ground-state atoms and one Rydberg atom — or, equivalently, many atoms and one photon. Should other photons enter a volume already occupied by a Rydberg polariton, the blockade effect causes a violation of the EIT condition, so the photons are absorbed rather than transmitted. Note that if the atom density is low, as in previous experiments[6], the absorption probability may still be small.

The final, essential ingredient needed to generate strong photon–photon interactions at the two-photon level is an atomic cloud of such high density that when two or more photons enter a blockade volume, all but one are absorbed within that volume, leaving a single Rydberg polariton. This 'photon blockade' is the novelty of Peyronel and colleagues' study. Their experiment reveals that a multi-photon incident light beam is converted, within a few micrometres, into a beam of single photons, with a small (less than 0.09) probability that two photons will leave the atomic gas at the same time. Interestingly, even though their sample is large enough for several Rydberg polaritons to coexist, the authors find that (and explain why) only one photon at a time is found within the entire sample.

An exciting feature of this experiment is that there are several clear avenues towards improving the properties of the medium. Cooler, denser atomic gases and lasers that have a narrower frequency range would improve the EIT transmission to nearly 100% and reduce the overlap of photons from the single-photon source. A looming challenge is to reconfigure the experiment so that the two-photon nonlinearity delays rather than absorbs excess photons[6]. This type of nonlinearity, which preserves the number of photons, would be extremely useful for quantum-information purposes.

In one respect, Peyronel and colleagues have demonstrated a quality single-photon light source that has a rate of emission in the megahertz regime, as Dudin and Kuzmich have shown[9] using a related approach. The key capability of this experiment[2] — engineering strong photon–photon interactions at the two-photon level — should also lead to various other new possibilities. For example, single-photon switches, photon detectors of high quantum efficiency, and non-destructive photon detection can easily be foreseen as extensions of this work. The physics of strongly interacting photons has a bright future. ■

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SYSTEMS BIOLOGY

A cell in a computer

The small genomes of some bacteria could provide the first complete understanding of a biological system. A new computer model brings this goal closer, by calculating every process in a dividing *Mycoplasma* cell.

MARK ISALAN

It has long been a dream in biology to push reductionism to the limit: to describe a cell as a set of interacting components and to capture whole-cell behaviour in a computer model. A good model doesn't simply recapitulate the observed behaviours that are fed into it. Rather, the aim is to predict the unknown effect of any novel perturbation or mutation. Such goals are very ambitious because of the challenge of attempting to obtain quantitative information on every one of the cell's gene products and metabolites. Nevertheless, Karr *et al.*[1], writing in *Cell*, present the most comprehensive model of a bacterial cell cycle so far, built on the basis of individual molecules and their relationships. Impressively, the model can predict gene-expression levels and cell-replication times in the challenging context of mutations involving gene deletions.

Mycoplasma genitalium is a urogenital bacterial parasite that has only 525 genes, making it one of the smallest genomes of any independently dividing cell — for comparison, the gut bacterium *Escherichia coli* has around 4,000 genes. Because of their status as one of the 'simplest' cells, *Mycoplasma* species are rapidly becoming the most measured biological systems in history, and full descriptions of their molecular content, in terms of DNA, RNA, protein and metabolites, are available[2–4]. The cells are therefore considered to be the ideal target for whole-cell modelling[5].

What is striking about Karr and colleagues' model is the sheer ambition of its scale and its attention to detail. The authors retrieved (and in some cases retested) more than 1,900 experimentally derived cellular parameters, such as enzymatic reaction rates and protein-binding

affinities, from around 900 publications. They then combined these to make 28 sub-models of cellular processes, such as metabolism, protein translation and DNA replication. They used sub-models so that they could apply the appropriate modelling method for each process. In computational biology, this requirement has been neatly summarized[6] as "Don't model bulldozers with quarks". So the authors combined different modelling techniques involving varying levels of detail, to allow different factors — including dependence on deterministic reactions, known constraints, probability and random variability — to be applied where appropriate.

Crucially, the authors then used a computational trick to join up the sub-models (Fig. 1a). Models calculate variables — numbers that represent varying system states. And variables change according to sets of rules — the equations and parameters used to describe the system. The authors allowed each sub-model to calculate independently the values of a set of 16 variables at a time-step of approximately one second. They then combined these results, which generated a new set of variables, and the process was repeated in a loop. Thus, all the sub-models 'communicated' with one another and the cell's status was constantly updated and recalculated. Although this is an approximation, because in reality all processes happen simultaneously, the end results converged plausibly towards the decision to divide, which the authors assessed as the moment that the bacterial cell membrane 'pinched' together to form two new cells (Fig. 1b).

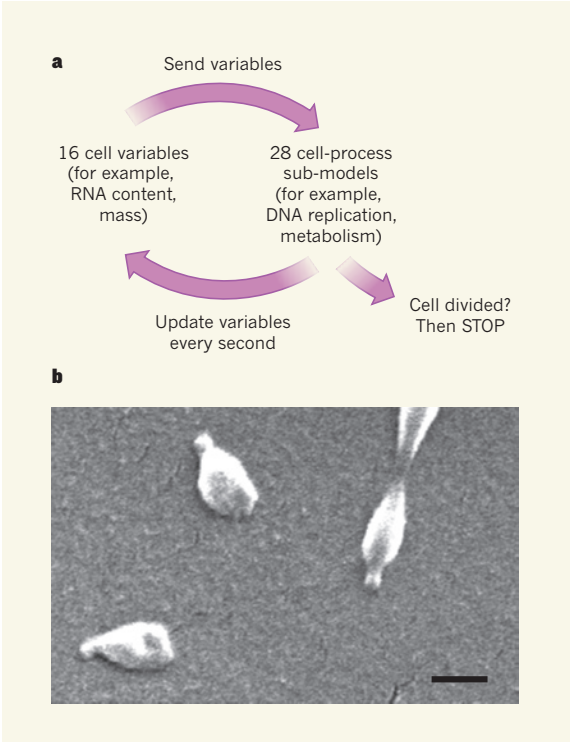

Figure 1 | Looping calculations to model cell division. **a**, Karr *et al.*[1] have constructed a computer model that attempts to calculate every process in *Mycoplasma genitalium* cells. Their modelling strategy involves 28 independent sub-models of cell processes, each incorporating different methods and levels of detail. The sub-models communicate by combining their calculations for 16 cell variables for approximately one second of the cell's life cycle, and then calculating the next second. The looping process culminates when cell division is induced. **b**, A scanning electron micrograph of *M. genitalium* cells, before (left) and during division (right). Scale bar, 0.5 micrometres.

After some optimization, the model produced estimates of metabolite concentrations, metabolism rates, and messenger RNA and protein levels, that were similar to experimental data. The model also allowed the authors to make several predictions about cell behaviour, including that 90% of the cell's genes will be expressed in the first 2.5 hours of the approximately 9-hour cell cycle. This prediction suggests that the chromosomes are 'explored' rapidly by gene-expression machinery. The key test, however, was whether higher-level system properties, such as the time taken for the cell to replicate itself, would be correctly predicted for bacteria carrying genetic mutations. When the researchers ran the model with each of the 525 genes individually deleted, they found that 284 of the genes are essential for cell survival and 117 are non-essential. These numbers are approximately 80% in agreement with experimental data for gene deletions that have been assessed previously.

The authors also tested the growth rates of 12 of the gene-deleted bacterial strains, and found 8 to be within the limits predicted by the model. In some of these cases, the experiments resolved discrepancies between the model and published growth rates, identifying, for example, a previously undescribed slow-growth mutant.

So, can the authors claim to have recreated a cell in a computer? They themselves say that the model should be compared to the first draft of the human genome, and be considered a work in progress. However, in modelling, discrepancies between predictions and experimental results are the key to improvements — they direct more detailed analyses and model refinement, and ultimately lead to better models. More challenging tests could be imagined. For example, could the model predict synthetic lethal mutants, in which the combination of two gene deletions will kill a cell, although either deletion alone permits survival? Furthermore, any model that attempts to predict phenotypes[7] (biological properties) from genotypes (gene sequences) will be subject to the problem that even genetically identical cells do not always give the same output. For example, random differences in the amount of chaperone proteins can 'buffer' mutations variably[8]. However, the *Mycoplasma* model can track such variability and therefore has the potential to predict these outcomes.

The metaphor of gene networks being connected in wiring diagrams is becoming commonplace and, even though such networks can be non-intuitive[9], they are ideal for computer modelling. Nevertheless, one of the most exciting ideas in studies of gene regulation is that network relationships may not always involve direct molecular interactions. For example, imagine a gene that is required for cell division — if there is low gene expression, the cell will not divide and so gene-expression levels will have longer to accumulate, which can create a feedback loop, or gene expression 'according to need'[10,11]. Fascinatingly, there is already a hint of this in one example from Karr and colleagues' model. They find that cell-cycle time is affected by the concentrations of DNA nucleotides (dNTPs), which are required for DNA replication. When dNTP levels are low, the cycle slows at the point of replication initiation, allowing dNTPs to build up, which then speeds up the rest of the cycle.

Extrapolating from such findings, I can imagine that similar feedback processes might exist for any cellular factor that contributes indirectly to reducing its own concentration. For example, factors for which transiently low concentrations reduce the activity of pathways for cell division, protein secretion or protein degradation might similarly self-regulate, restoring and buffering themselves over time. So perhaps the most exciting thing about a whole-cell model is that it may allow us to look beyond the direct molecular 'cogs and wheels' that drive biology and into the emergent properties of biological systems. ■

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