Understanding gene expression variability in its biological context using theoretical and experimental analyses of single cells

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Summary

Understanding gene expression variability in its biological context using theoretical and experimental analyses of single cells

Traditional gene expression studies have largely ignored cell-to-cell variability in transcription. Current methods allow for single cell analyses and have shown considerable variability in gene expression, even in populations of isogenic cells being exposed to the same growth environment. In this thesis, we assess the impact of various parameters of gene expression variability using experimental systems that enable quantification of the gene expression status of single cells. Based on the obtained data we parameterized mathematical models of gene expression.

In the first two chapters we focused on the effects of cellular volume growth on gene expression. Cell growth largely relates to an increase in cellular volume and the amount of nuclear DNA, i.e. in the interphase of the cell cycle cells double their cellular volume and DNA, and in mitosis they divide into two daughter cells. In general, the concentrations of reactants dictate the reaction rates of the chemical reactions inside cells. This means that to keep protein production constant in a cell, the number of mRNA molecules (and other reactants) need to increase at the same rate as cellular volume. However, gene expression variability is traditionally quantified in absolute numbers by quantifying mRNA copy numbers, which ignores the impact of cellular growth.

We combined single-cell mRNA expression levels with cell volume measurements and observed that the number of mRNA molecules scales proportionally with cell volume. This means that biologically relevant transcription variability (based on mRNA concentrations) is much lower than generally determined by single-molecule mRNA analysis that only takes transcription counts into consideration. The proportionality between mRNA numbers and cell volume implies that the mRNA concentration remains homeostatic over the course of the cell cycle. This indicates that regulatory mechanisms are in place to counteract both the dilution of DNA concentration when cells grow and the doubling of DNA during DNA replication. Our data show the importance of measuring cell growth in combination with gene expression cell-to-cell variability. Hence, it is crucial to understand how cells grow and to measure how growth affects gene expression. We combined experimental data and a theoretical framework of bacterial cell cell growth to construct a model to analyze gene expression in a growing population of cells. The obtained simulations were validated with an experimental setup that combined cell growth measurements with protein measurements in bacterial cells. This algorithm is implemented in StochPy (a python simulation package), which can now be used for simulations and analyses of gene expression networks in growing cells.

In chapter 2 we observed the effects of local chromatin structure in which genes are embedded on gene expression variability. This cell-to-cell variability can only be explained by changes

in the dynamics of the expression model. In the fourth chapter we describe how we modified the chromatin environment of a reporter gene and measured synthesized transcripts in real time when inducing transcription inactivation of the activated reporter gene. We observed that reporter gene inactivation is preceded by a delayed response and that targeting a chromatin regulatory protein (epigenetic reader protein methyl-CpG binding protein-2) to the reporter gene accelerates the response to signals suppressing active transcription.

In chapter 5 we demonstrate the effects of UV-damage on gene expression. We quantified nuclear single-molecule mRNA numbers to determine the UV-damage-induced transcription changes at the single gene level. Our approach enabled us to determine the relationship between UV-dose, gene size, transcription recovery, and DNA repair at the single gene level. Since the probability on gene damage is proportional to its length, gene length is an important parameter for UV damage-induced transcription stalling. By measuring the recovery of transcription after UV-exposure we were able to estimate the half-life of DNA damages. Intriguingly, we observed two distinct half-lives of DNA damage depending on the UV-dose supporting recent observations that transcription coupled and global DNA repair pathways can be discriminated by exposing cells to a defined UV-dose.

In chapter 6 we studied the effect of gene expression variability in breast cancer cells. Although relapse to treatment is observed in up to 30-40% of patients, the exact mechanism involved is unknown. It is expected that changes in the expression level of aromatase induces resistance and stimulates tumor progression. We demonstrate that in breast cancer cells treated with aromatase inhibitors, a subpopulation of cells overexpresses aromatase. Our data suggest that treatment resistance may be initiated by a subset of cells with an altered expression status. Overall, we analyzed gene expression variability in dynamic cells and environments and demonstrate how single cell techniques can be utilized to understand gene expression variability.

Samenvatting

Begrip van variabiliteit in genexpressie door middel van theoretische en experimentele studies van individuele cellen

In traditionele studies naar genexpressie werden verschillen tussen individuele cellen in een populatie niet opgemerkt. Recent ontwikkelde technieken maken het mogelijk verschillen tussen de cellen te meten. Dergelijke studies waarin enkele cellen worden gemeten laten een grote variatie in genexpressie tussen de cellen zien, zelfs in celpopulaties die genetisch identieke zijn en die in een identieke omgeving groeien. In dit proefschrift bestudeerden we de rol van verschillende parameters op de variatie in genexpressie en hoe deze parameters het functioneren van individuele cellen beïnvloedt. In onze studies hebben we onder andere gebruik gemaakt van een microscopische techniek waarmee we het exacte aantal mRNA's in een cel kunnen kwantificeren. De verkregen data gebruikten we om met wiskundige modellen genexpressie te simuleren om de verkregen data beter te begrijpen.

In de eerste hoofdstukken bestudeerden we hoe volumeverandering (celgroei) de variatie in genexpressie beïnvloedt. Tijdens celgroei neemt het volume van de cel, maar ook de hoeveelheid DNA in de celkern toe. In het algemeen is de bijdrage van concentraties van moleculen die reacties aangaan, de belangrijkste factor voor de snelheid waarmee een reactie in de cel verloopt. Om reactiesnelheden constant te laten verlopen, zouden alle reagerende moleculen en het volume van de cel met dezelfde snelheid moeten toenemen. Het belang van een veranderd aantal moleculen in de cel hangt dus ook sterk samen met andere parameters van de cel, zoals onder andere het volume van de cel. Het is opmerkelijk dat conventionele studies die genexpressie bestuderen alleen het aantal mRNA moleculen in de cel analyseerden en de invloed van bijvoorbeeld celgroei negeerden.

In dit proefschrift hebben we in individuele cellen zowel de hoeveelheid mRNA als het celvolume bepaald. In deze metingen hebben we waargenomen dat de hoeveelheid mRNA (van 'ongereguleerde' genen) proportioneel toeneemt met het celvolume. Dit impliceert dat de hoeveelheid biologisch relevante variabiliteit in genexpressie veel lager is dan in het algemeen gemeten wordt, wanneer alleen het aantal moleculen in ogenschouw wordt genomen. Daarbij impliceert de geobserveerde proportionaliteit ook dat de mRNA concentratie constant blijft tijdens een celcyclus. Dit geeft aan dat er tijdens celgroei genregulatie plaatsvindt om de verdunning van de concentratie DNA, maar ook de verdubbeling tijdens DNA replicatie tegen te gaan. Om meer inzicht te krijgen in deze afhankelijkheid tussen celgroei en genexpressie hebben we een model gegenereerd waarin deze processen zijn gekoppeld. De met het model uitgevoerde simulaties hebben we gevalideerd aan de hand van experimentele data van (eiwit)expressie en celvolume-data van individuele bacteriën. Dit algoritme is geïmplementeerd in StochPy (een python simulatietool) en het kan nu gebruikt worden voor het analyseren van genexpressie netwerken in groeiende cellen.

Naast het verband tussen mRNA expressie en celvolume, hebben we op basis van de bevindingen in hoofdstuk 2 ook geconstateerd dat de lokale (chromatine) structuur waarin genen zich bevinden, effect heeft op de variabiliteit in genexpressie. De bevindingen impliceren dat de samenstelling van het genoom en epigenoom lokaal rond een gen een bijdrage levert aan hoe het expressie model zich gedraagt. In hoofdstuk 4 hebben we genexpressie bestudeerd in 'real-time' na het deactiveren van genexpressie van een reporter gen als celsysteem. We observeerden dat de reactietijd van het celsysteem waarin we onze metingen verrichten afneemt wanneer we de lokale samenstelling van het chromatine waarin het reporter gen zich begeeft veranderden (d.m.v. MeCP2 'targeting').

In hoofdstuk 5 gebruikten we 'Single Molecule mRNA FISH' om het effect van UV straling op genexpressie te meten. We bestudeerden de relatie tussen de hoeveelheid UV-blootstelling, de afmeting van een gen en het herstel van genexpressie na DNA reparatie. Omdat de kans op UV schade afhankelijk is van de afmeting van een gen, is genlengte een belangrijke parameter voor het effect van UV-blootstelling op het uitzetten van genexpressie. Zoals we hadden verwacht, hebben we een grote mate van variabiliteit in genexpressie activiteit na UV-blootstelling gemeten. Door het herstel van genexpressie na UV-blootstelling te meten in combinatie met een eenvoudig model waarmee dit proces wordt gesimuleerd, konden we de 'half-life' van DNA-schade incidenten in genen vaststellen. Wij observeerden dat de tijd waarin schade wordt hersteld afhankelijk is van de ernst van de UV-blootstelling. Deze bevindingen zijn in overeenstemming met recente bevindingen dat er verschillende reparatie mechanismen zijn om DNA schade die door verschillende hoeveelheden UV-blootstelling (i.e. hoge of lage dosis) wordt veroorzaakt, te herstellen,

In het laatste hoofdstuk hebben we het effect van variatie in genexpressie in borstkanker cellen bestudeerd. 30 tot 40% van de borstkanker patiënten die gediagnosticeerd zijn met hormoongevoelige borstkanker worden naar verloop van tijd ongevoelig voor de hormoontherapie (zoals aromatase inhibitoren). De precieze veranderingen waardoor de behandelde borstkanker cellen niet meer op de hormoontherapie reageren, is nog vrijwel onbekend. Recente bevindingen wijzen erop dat de behandelde cellen het effect van de hormoontherapie behandeling (aromatase inhibitoren) omzeilen door de expressie van aromatase te verhogen. Dit zorgt voor ongevoeligheid voor de hormoonbehandeling en leidt tot uitgroei van de tumor. Onze bevindingen laten zien dat verhoogde aromatase expressie aanwezig is in een subpopulatie van de behandelde borstkanker cellen. Dit suggereert dat de resistentie tegen de behandeling geïnitieerd word door slechts enkele cellen.

In dit proefschrift hebben we op verschillende manieren de variabiliteit in genexpressie bestudeerd. We hebben laten zien hoe het analyseren van individuele cellen in veranderlijke condities kan bijdragen aan het begrijpen van de consequenties van variabiliteit in genexpressie.

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List of publications

1. Explaining the enigmatic K_M for oxygen in cytochrome c oxidase: A kinetic model.
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6. Cell-to-cell transcriptional variability as measured by single molecule RNA FISH to detect epigenetic state switching.
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   Submitted

7. Statistics and simulation of growth of single bacterial cells: illustrations with *B. subtilis* and *E. coli*
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8. MeCP2 accelerates the transition rate of transcription repression dynamics measured at a defined chromatin locus in single cells.
   Kempe H*, Piebes DGE*, Vuist IM, van Belle GJ, Houtsmuller AB, Verschure PJ.
   Manuscript in preparation

9. Transcription recovery after UV-C-induced DNA damage: the relationship between UV-C dose, gene size and DNA repair at the single gene level.
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   Manuscript in preparation

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