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Probabilistic mapping of the sub-cellular proteome

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Abstract: In biology, localisation is function - understanding the sub-cellular localisation of proteins is paramount to comprehend the context and full extend of their functions. Shotgun mass spectrometry-based spatial proteomics method are orthogonal to widely used targeted microscopy-based assay. In conjunction with contemporary machine learning, the former enable to build proteome-wide protein localisation maps, informing us on the location of thousands of proteins. When studying these proteome-wide spatial maps, one can learn that while some proteins can be found in a single location within a cell, up to half of the proteins may reside in multiple locations, can dynamically re-localise, or reside within an unknown functional compartment, leading to considerable uncertainty in associating proteins to their sub-cellular location. Recent Bayesian modelling approaches enable us to mine these data, and in particular the dynamic fraction of the spatial proteome, in much greater depth. We are now in a position to (1) probabilistically model protein localisation as well as quantify the uncertainty in the location assignments, and (2) compute a probability for, and quantify uncertainty in, whether a protein is differentially localised upon cellular perturbation. These computational approaches lead to better and more trustworthy biological interpretation of these rich spatial proteomics data.

Acknowledgements

- Mr Oliver Crook
- Dr Lisa Breckels

Outline

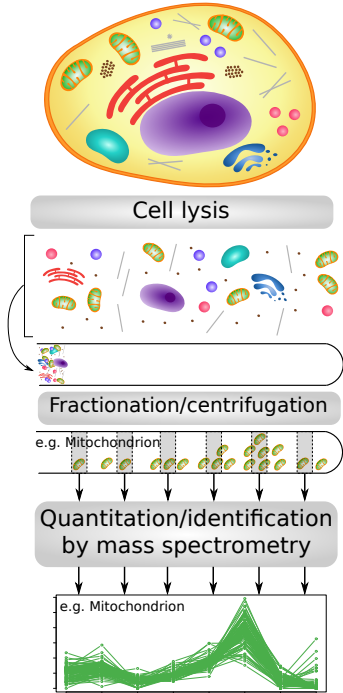# Cell organisation - **localisation is function**
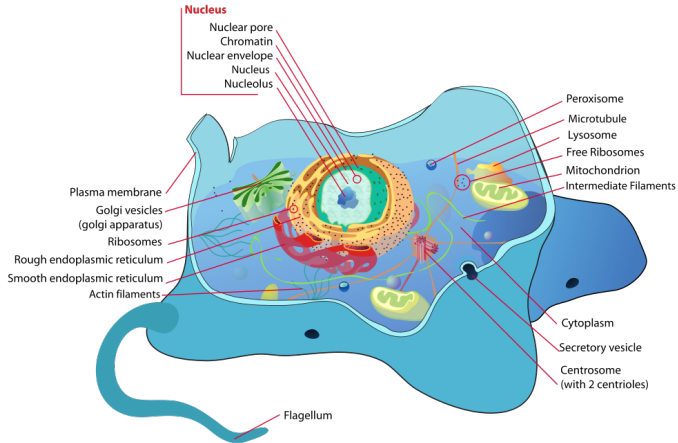
Spatial proteomics is the systematic study of protein localisations.

Localisation − re-localisation − mis-localisation

Image from Wikipedia http://en.wikipedia.org/wiki/Cell_(biology).

Explorative/discovery approaches, steady-state **global localisation maps** (as opposed to microscopy-based targeted approaches).

Density gradient: PCP (Dunkley et al., 2006), LOPIT (Foster et al., 2006), hyperLOPIT (Christoforou et al., 2016; Mulvey et al., 2017) and **Differential centrifugation** Itzhak et al. (2016), LOPIT-DC (Geladaki et al., 2018).

Cell lysis

Fractionation/centrifugation

e.g. Mitochondrion

Quantitation/identification by mass spectrometry

e.g. Mitochondrion

Quantitation data

	Fraction$_1$	Fraction$_2$	$\ldots$	Fraction$_L$
$\mathbf{x}_1$	$x_{1,1}$	$x_{1,2}$	$\ldots$	$x_{1,L}$
$\mathbf{x}_2$	$x_{2,1}$	$x_{2,2}$	$\ldots$	$x_{2,L}$
$\mathbf{x}_3$	$x_{3,1}$	$x_{3,2}$	$\ldots$	$x_{3,L}$
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
$\mathbf{x}_i$	$x_{i,1}$	$x_{i,2}$	$\ldots$	$x_{i,L}$
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
$\mathbf{x}_N$	$x_{N,1}$	$x_{N,2}$	$\ldots$	$x_{N,L}$

Quantitation data and organelle markers

	$Fraction_1$	$Fraction_2$	...	$Fraction_L$	markers
$\mathbf{x}_1$	$x_{1,1}$	$x_{1,2}$	...	$x_{1,L}$	unknown
$\mathbf{x}_2$	$x_{2,1}$	$x_{2,2}$	...	$x_{2,L}$	loc_1
$\mathbf{x}_3$	$x_{3,1}$	$x_{3,2}$	...	$x_{3,L}$	unknown
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
$\mathbf{x}_i$	$x_{i,1}$	$x_{i,2}$	...	$x_{i,L}$	loc_k
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
$\mathbf{x}_N$	$x_{N,1}$	$x_{N,2}$	...	$x_{N,K}$	unknown

Outline

Visualisation
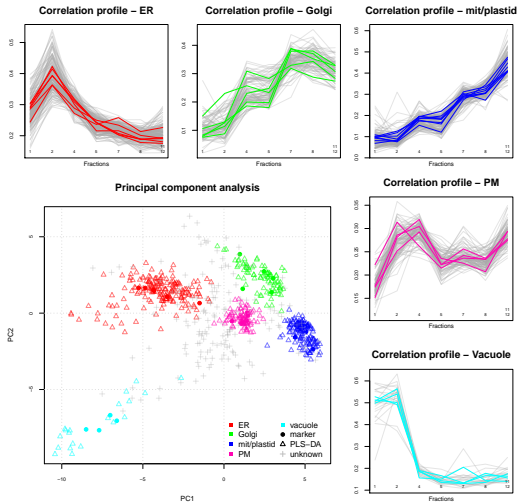

Figure: From Gatto et al. (2010), *Arabidopsis thaliana* data from Dunkley et al. (2006)
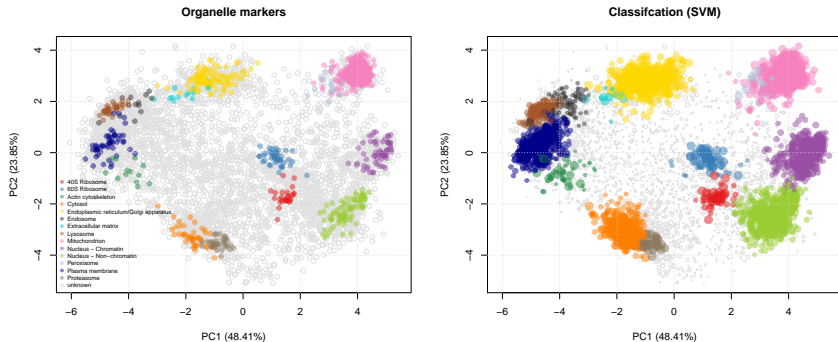
Figure: Support vector machines classifier (after 5% FDR classification cutoff) on the embryonic stem cell data from Christoforou et al. (2016).

Outline

Computational challenges

- Visualisation (cluster, unsupervised learning)
- Classification (supervised learning)
- **Novelty detection** (semi-supervised learning)
- Data integration (transfer learning)
- **Unvertainty quantification**
- **Multi-localisation**
- **Spatial dynamics**

To uncover and understand biology

Outline

Novelty detection

Outline

Multi-localisation

Outline

Spatial dynamics

Outline

Behind the scences

References I

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Thank you for your attention

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