

# Principles of Electronic Nanobiosensors

Unit 5: Putting the Pieces Together

Lecture 5.3: Genome Sequencer III

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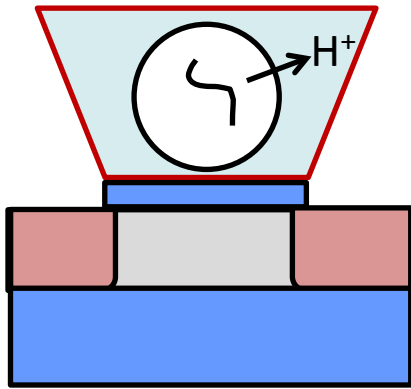
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# Outline

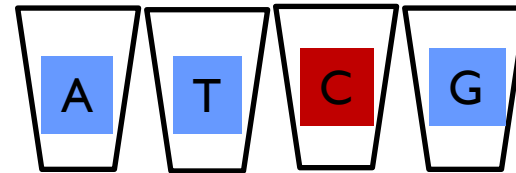
- Challenges of Selectivity and sequencing
- Signal amplification by PCR
  - Classical PCR
  - Emulsion PCR
- Signal degradation by
  - $n=2$  systems
  - Homopolymer sequencing
  - Well-to-well cross talk
  - Salt degradation of MOSFET
  - Signal, noise, and scaling
- Putting the pieces back together
- Conclusions

# Recall: Sequencing by synthesis

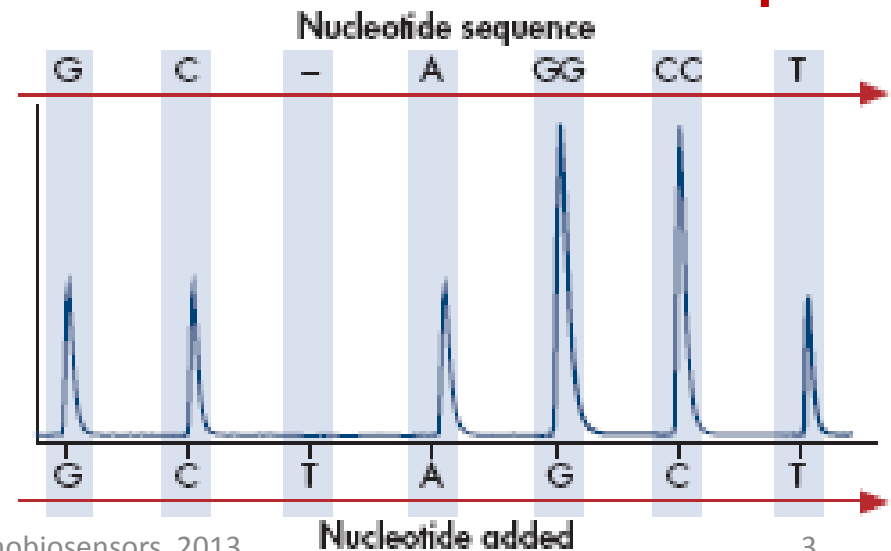
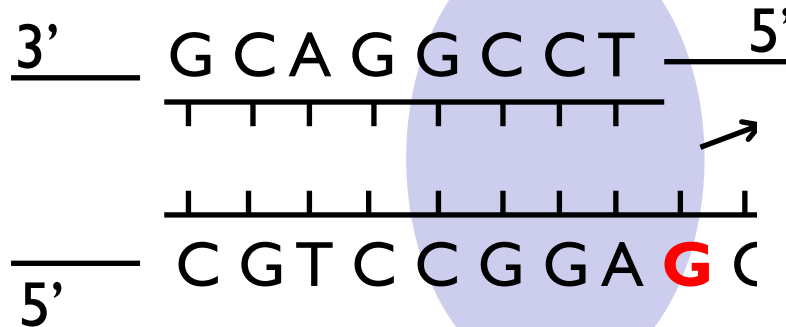


Cycle the letters!

Sequential Addition/washing

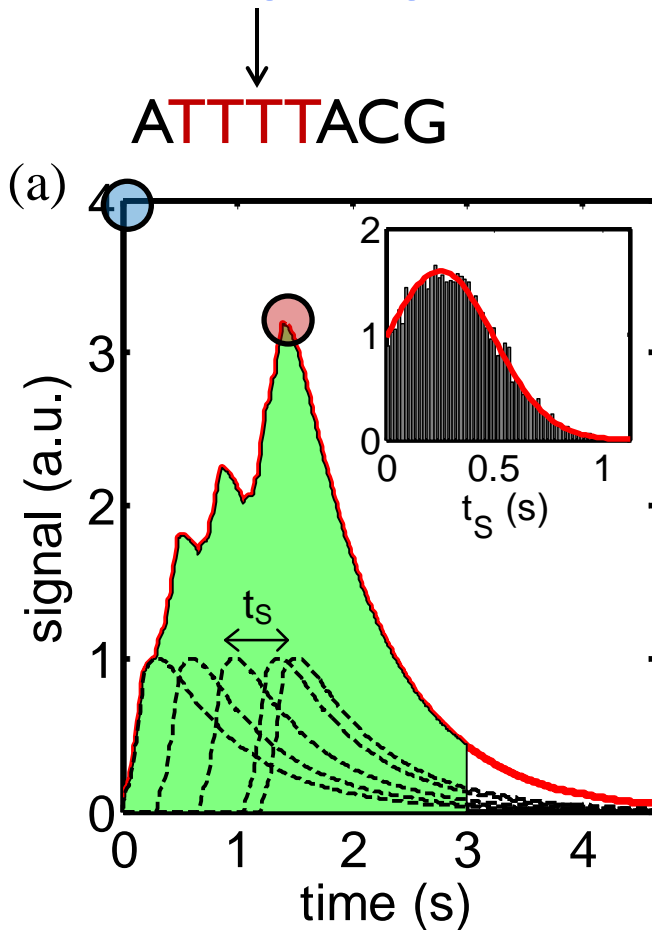


Polymerase



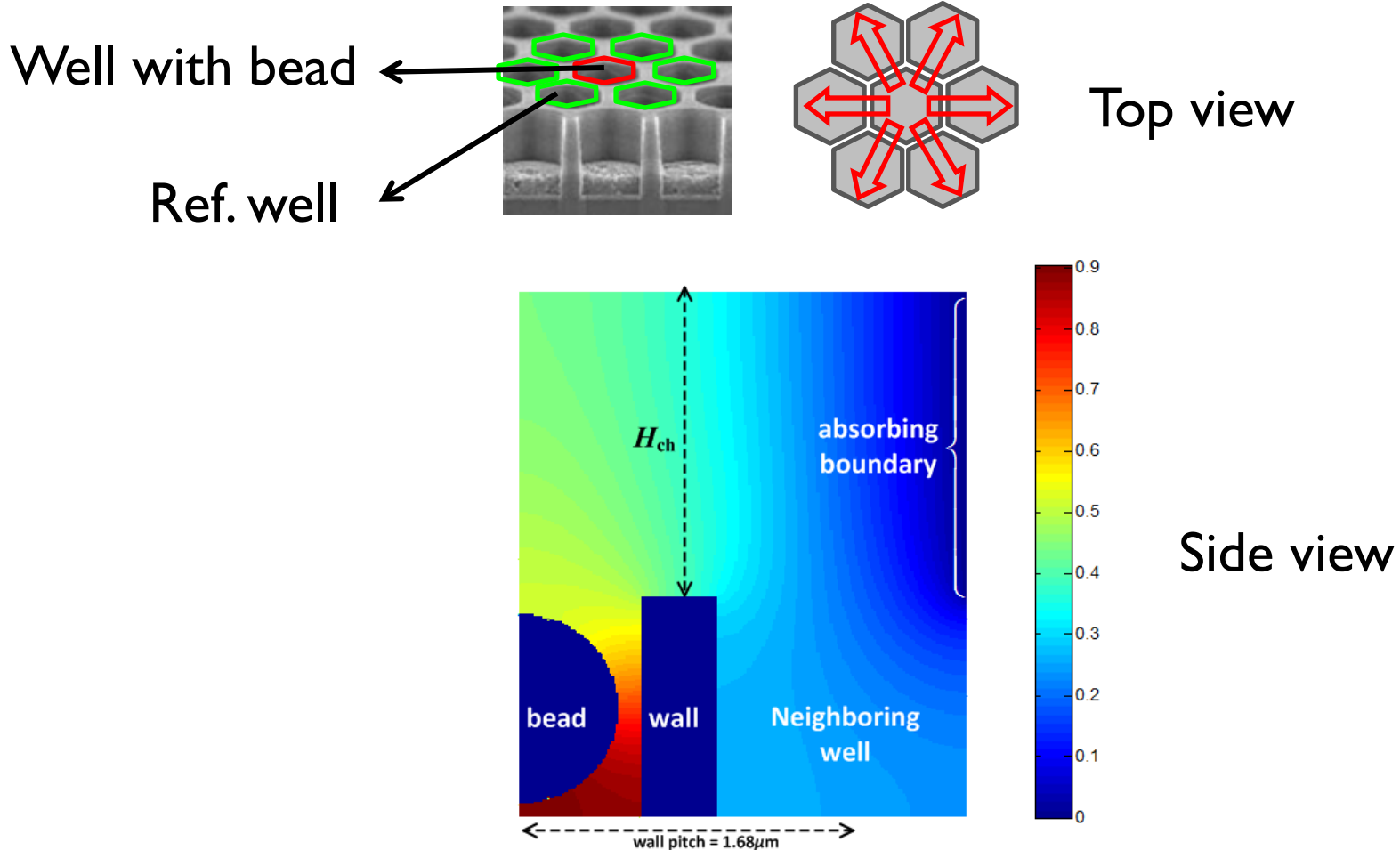
**Pulse of protons when correct is base is incorporated**

# Homo-polymer Error (~3% for N=5)



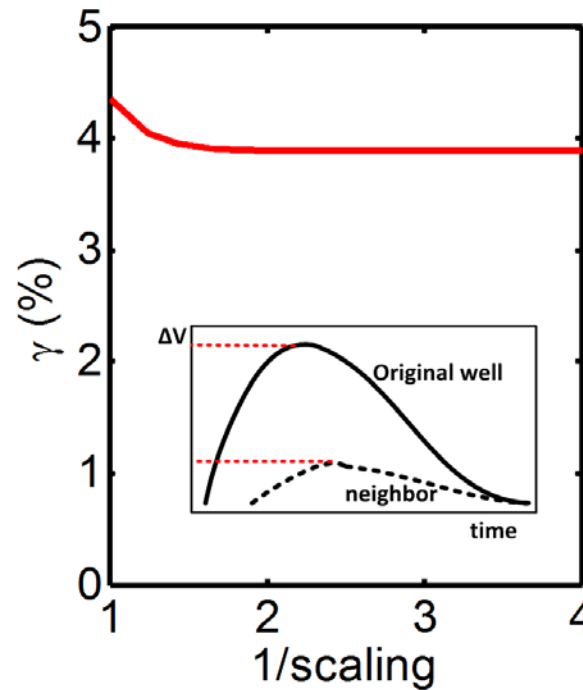
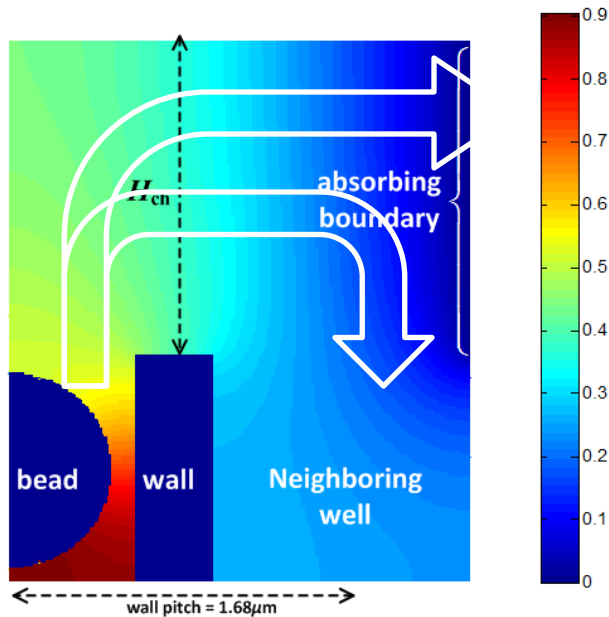
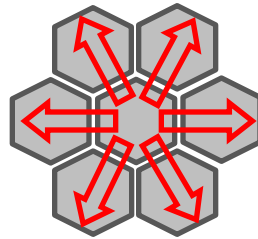
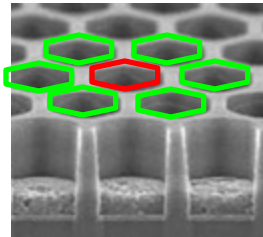
Peak suggests TTT, actually TTTT

# Signal and Reference Well



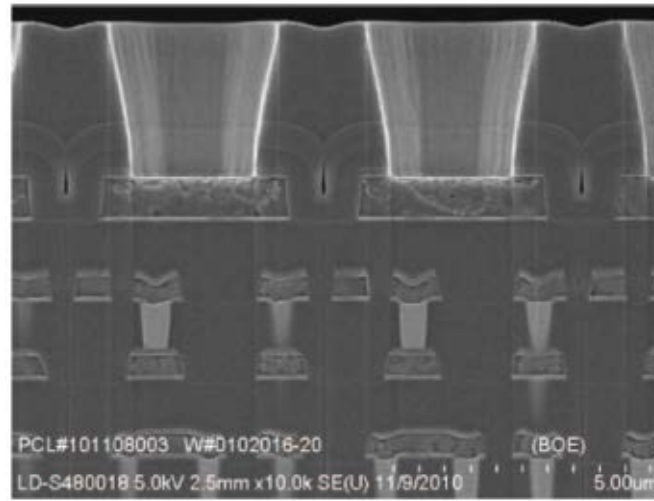
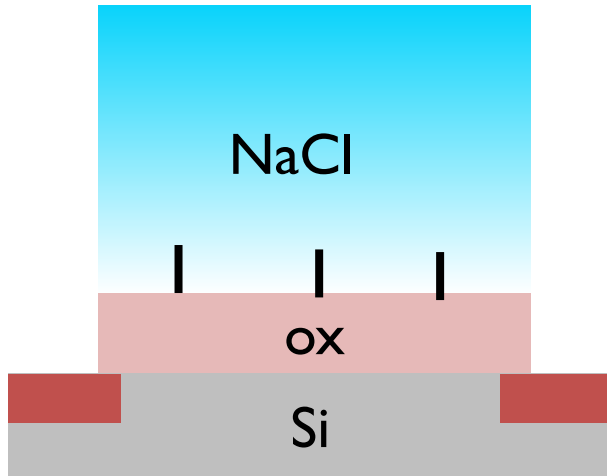
The reference well must not be contaminated by transient signals

# Scaling of Cross-Talk



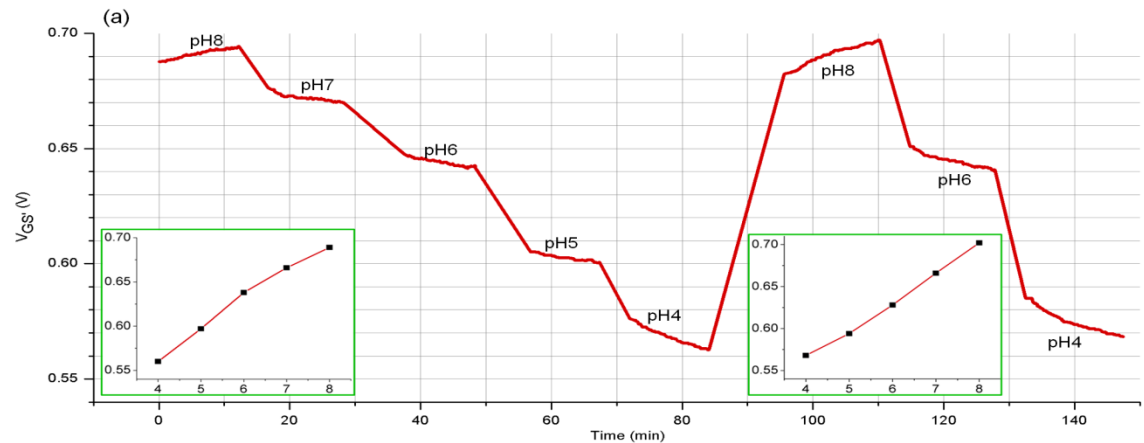
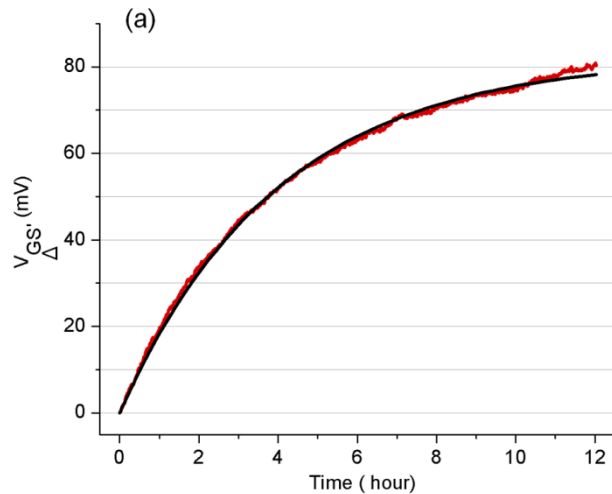
Cross-talk between nearby wells and the corresponding signal contaminations is negligible.

# Reliability: Salt Instability addressed



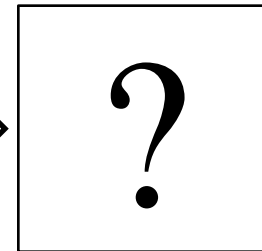
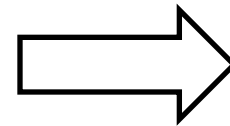
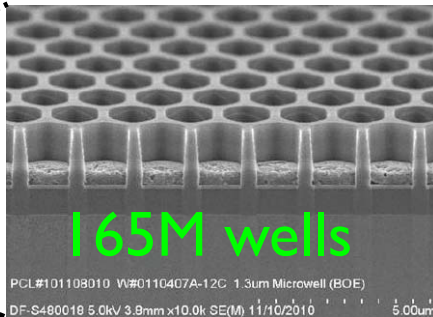
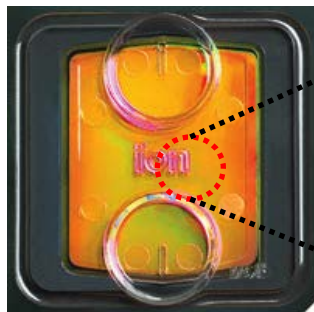
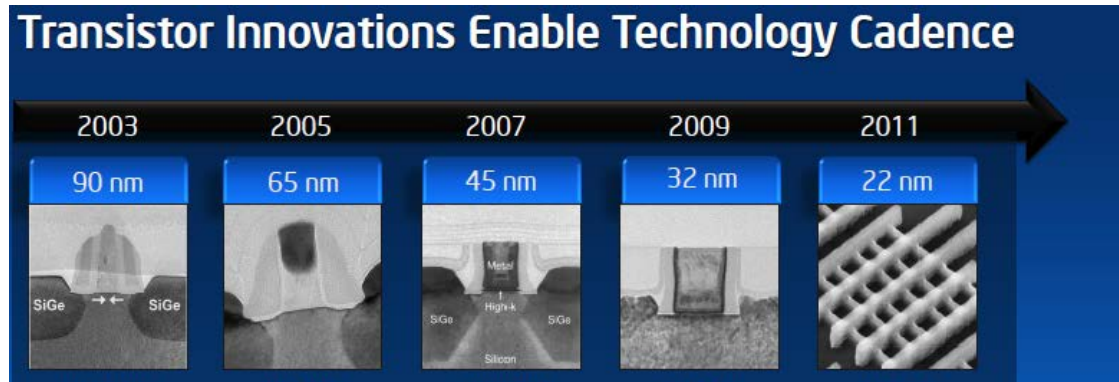
Extended gate

Salt never in contact with the transistor.



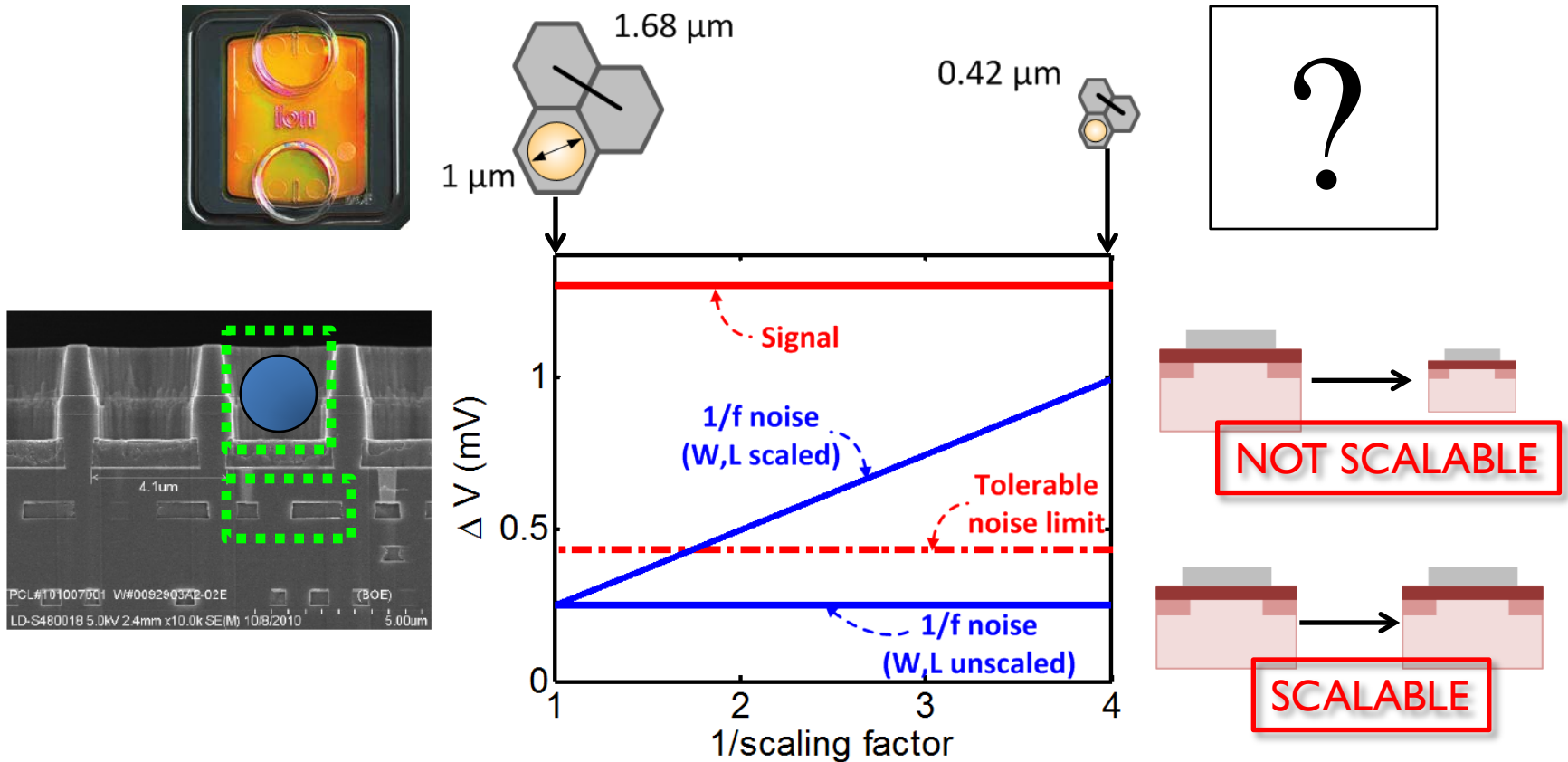
Most devices does not remain stable for > 2-3 hrs

# Scaling challenges of Sequencing Chips



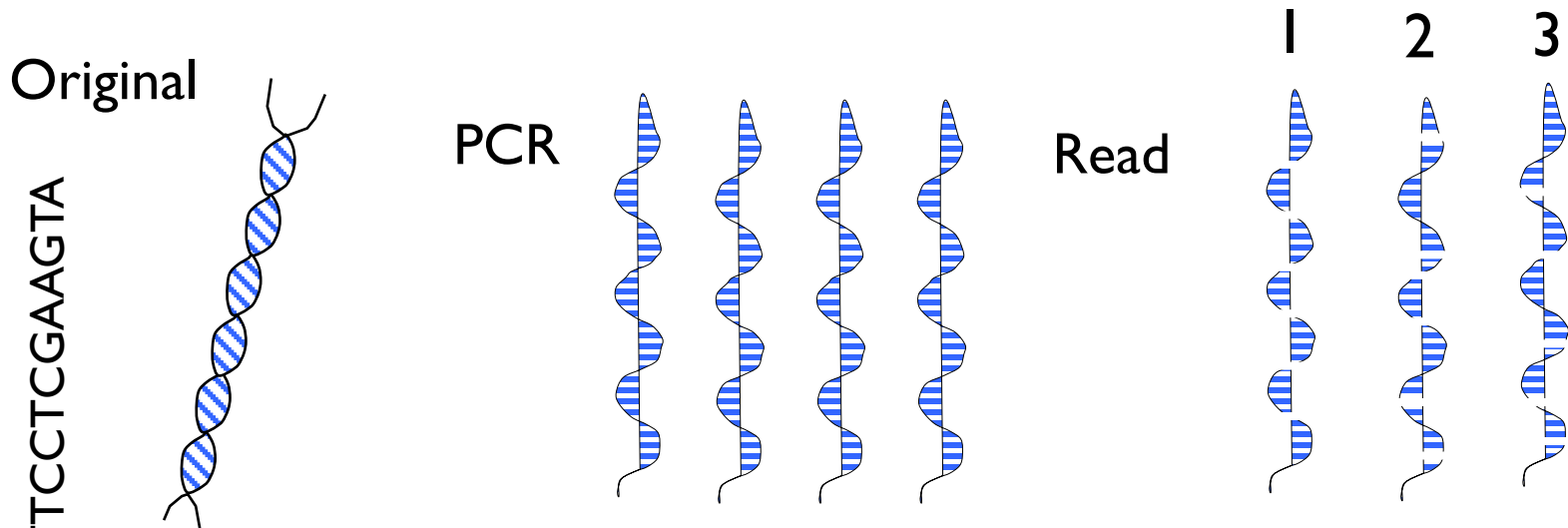
Can we predict the scaling properties?  
What are the challenges in scaling-down?  
Will we meet a scaling limit in near future?

# Properties of Signal and Noise Scaling

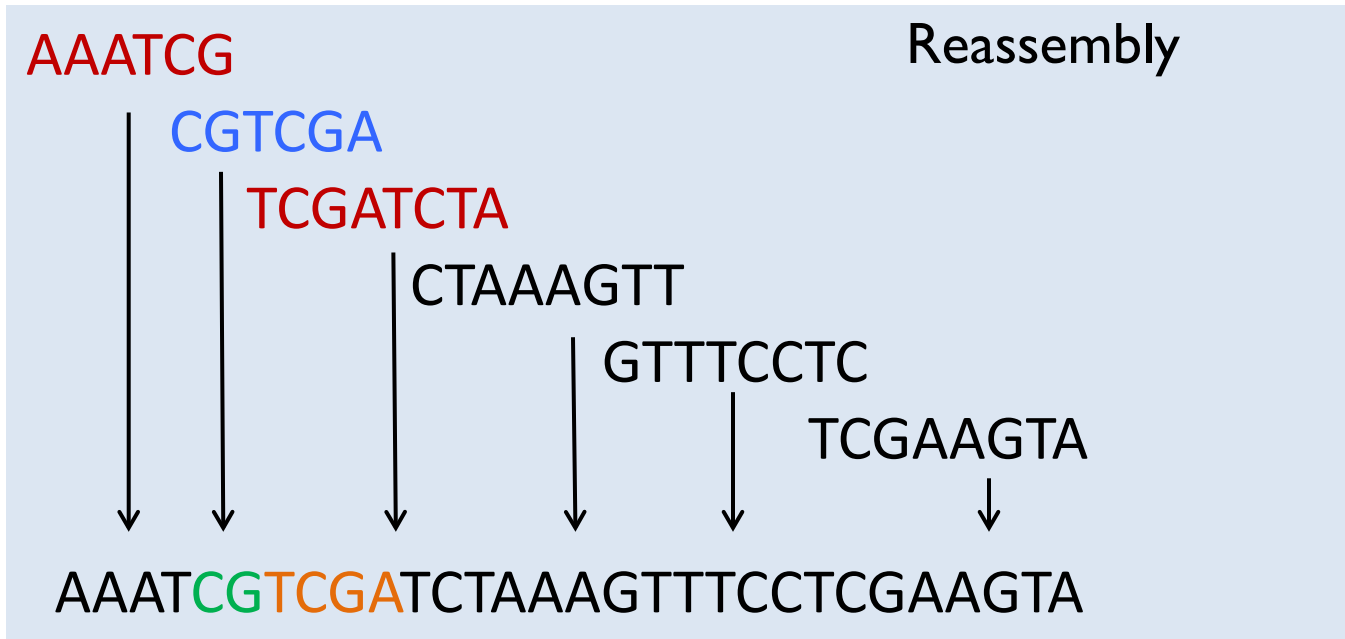


Given the size of wells/beads and that of MOSFETs,  
Ion Torrent's pH sequencing chips are scalable.

# Putting together the pieces



AAATCGTCGATCTAAAGTTTCCTCGAAGTA



# Conclusions

- pH-based genome sequencers may provide comparable sequencing performance at a lower cost.
- Like MOSFETs, the scaling properties offer many surprises. The chips can be scaled down so long the size of MOSFETs remain invariant.
- The cross-talk among the wells is insignificant.
- Simple analysis explains the origins of inefficiency of bead loading inefficiency and error in homo polymer sequencing.
- New generation of sensors may have to rely on super Nernst sensors.

# References

- Rothberg, Jonathan M., et al. "An integrated semiconductor device enabling non-optical genome sequencing." *Nature* 475.7356 (2011): 348-352.
- Margulies, Marcel, et al. "Genome sequencing in microfabricated high-density picolitre reactors." *Nature* 437.7057 (2005): 376-380.
- Glenn, Travis C. "Field guide to next-generation DNA sequencers." *Molecular Ecology Resources* 11.5 (2011): 759-769.
- Quail, Michael A., et al. "A tale of three next generation sequencing platforms: comparison of Ion Torrent, Pacific Biosciences and Illumina MiSeq sequencers." *BMC genomics* 13.1 (2012): 341.
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