The Ampere prize 2018 for Young Investigators

Prof. Dr. Katja Petzold has received the AMPERE prize for Young Investigators during the EUROMAR conference in Nantes, France. The prize was given "in recognition of her achievements in using solution-state NMR for the study the molecular mechanism of RNA function".

The German biochemist has already in her PhD (Umeå University Sweden, graduated in 2009) worked with dynamics in RNA (1) and developed new pulse sequence (2), before she moved, after a short stay in South Africa to dip her toes into drug development, for her post-doctoral fellow to the group of Prof. Al-Hashimi to the University of Michigan, USA, from 2010 to 2013. In 2014 she was appointed Assistant Professor at the Karolinska Institute, Stockholm, Sweden, where she was recently promoted to Associate Professor.

Petzold studies structure and dynamics of RNA with focus on RNA based diseases by applying relaxation dispersion NMR. She has been working with a number of biological systems, where she could demonstrate invisible, low populated states that are of relevance to the function of these RNAs, e.g. the dimerization initiation site of the SL1 in HIV (1). She could further show, that dynamics in RNA are not limited to structural changes, but even chemical changes are existing as low-populated states, that can influence translation, in the found keto-enol tautomer present in RNA GU wobble base-pairs (2). She has since established a broad spectrum of RNAs under investigation, from microRNA (5), to Hepatitis B virus RNA up to ribosomes, where she uses her expertise in method development to push the limits of current methods (6) to discover and understand the importance of these invisible states. In collaboration with several groups from a variety of disciplines, she creates new routes to measure high-resolution dynamical structural ensembles with an NMR informed MD approach. Further, her lab tests structural hypothesis and function of these invisible states in human cell-lines, together with molecular biologists, and even mice to develop a biological relevant structure determination process.

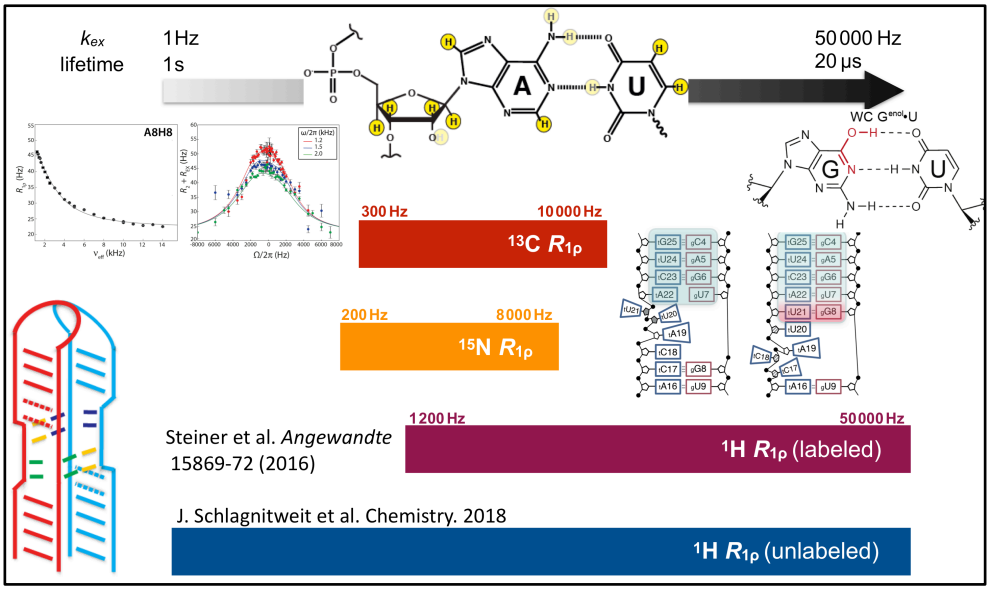

Figure: An overview of methods available to detect invisible states of RNA with examples of these states. Highlighted here is the expansion of the measurement timescale by the use of ^{1}H relaxation dispersion to cover basically the whole µs to ms timescale of chemical exchange. Invisible states visualized are: bottom left: the dimerization initiation site dynamics leading to a zipper like motion, allowing two homo-dimers to perform a strand exchange switching one base-pair at a time. Upper right: the keto-enol tautomer, that converts simple GU wobble base-pairs into Watson-Crick look alikes, increasing the potential for misincorporation during translation. Middle right: the extension of an microRNA seed recognition by a single base-pair switch, that pushes the actor protein, Ago, from the screening mode into the active mode.

In her talk at the EUROMAR in Nantes "Capturing Transient States in RNA", Petzold presented new ^{1}H relaxation dispersion NMR experiments (RD) and invisible states found with the extensive toolbox developed.

The new ^{1}H RD allows to extend the timescale to be probed by NMR from the lower ms to the high-end of the µs timescale and therefore detect many more chemical exchange processes. Additionally, the latest experiment allows to omit the use of expensive heteronuclear labeling, making RD experiments affordable and feasible (samples can be simply bought and one does not require an own RNA production setup) for a large number of people. At the same time the experiment became more sensitive, as the R_2 increase caused by the attached heteronuclei disappears and hindering couplings vanish.

Using these experiments she revealed invisible states in RNA-RNA complexes, specifically on a microRNA (miR) binding its messenger RNA (mRNA) target. MiR

finds it target by searching for a 5-8 nucleotide long Watson-Crick complimentary sequence on the mRNA, called seed, binding it in a perfect Watson-Crick base-paired helix. miR-34 binds mRNA of Sirt1, a regulator of P53 by deacetylation, via a 6/7 nucleotide seed, while in an invisible state, this seed gets extended by an additional base-pair stabilizing the previously weak closing base pair to a complete 8 nucleotide seed. We hypothesize that with this conformational change of the RNA, miR-34a bound to mSirt1 overcomes a binding hurdle of the effector protein Argonaut (Ago), causing an induced fit change from a screening state into an active mode, confirmed by an increase of activity of Ago by stabilization of this previously invisible state.

References:

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