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The R&D Value Cycle of Nano-Enabled Medical Devices – The Case of Biosensors

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Nano-enabled devices leverage two general phenomena that occur at the nano-scale: (a) transitions in physiochemical properties, and (b) transitions in biochemical interactions. Evidently, the R&D value cycle is very scientist-driven, revolving around university departments generating new opportunities for transfer of instrumentation and techniques across disciplinary boundaries in order to formulate a proof-of-concept into a successful interaction with the industry that will attain its market integration. This paper uses biosensors as an exemplar to study the dynamic structure of this innovation system, in an attempt to frame it by considering (i) its scientific basis, towards (but not through) its commercial applications (within-academy R&D), and (ii) the factors intrinsic to the technology itself (technology barriers) that could ultimately determine its rate of commercialization (R&D transfer from academy to industry). The results indicate that different research strategies decided upon at the academy level can enhance or thwart industry's ability to appropriate the value of the university output, whereas market-oriented technology trajectories and roadmaps drawn at the industry level can increase uncertainty and risk if the diffusive and elusive nature of academic research is neglected.

1. The university-industry linkages at the nanotechnology era

The medical device industry, highly dynamic and diverse, is at the forefront of research and public interest for more than three decades now. The distinctive features of this industry are (i) a high demand-driven absorptive capacity, i.e., a marked science-based value, drawn from the need to rapidly recognize, appraise and assimilate exogenous technological change within its scope of research (Bishop et al., 2011), and (ii) a high supply-driven transformative capacity, i.e., a marked market-based rate of return in the endogenously generated knowledge, drawn form the need to constantly redefine the portfolio of its products (Allarakhia and Walsh, 2011). The strong relationship between innovation and competitiveness sets intense university-industry alliances, numerous academic spin-offs, and multidisciplinary collaborations with a view to translating proofs-of-concept to hand-held devices, implantable monitors, or molecular diagnostics platforms (Guan and Zhao, 2013). To no surprise, nanotechnology has been early apprehended as a discontinuous and disruptive technology at an era of ferment, i.e., as an innovation system that results in the generation of new technologies and the revisiting of existing ones (Nicola et al., 2013), presenting superior performance and market trajectories along critical dimensions that customers (i.e., health care providers and patients) value (Kostoff et al., 2005).

The impact of nanotechnology on clinical diagnostics is a case in point. The scale-length reduction that has been achieved through nanosynthesis (bottom-up technology) and nanomachining (top-down technology) provided a variety of products already in the market and countless opportunities for point-of-care, non-invasive or implanted miniaturized monitors, personalised drug delivery systems or artificial organs. Patent applications in the biomedical sector witnessed an annual growth rate of 15 % for the period 1996 to 2002, which rapidly escalated to 28 % thereafter (Delgado, 2010). Markedly, the number of patents filed by academic institutions is comparable to those of the private sector, whereas the former obtained higher values for importance of innovations, generality of research outcomes, and for reliance on scientific sources, indicative of the stronger focus on basic research maintained by universities (Sapsalis et

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al., 2006). The impact of the knowledge exploration path, assumed by the academy, to the technology exploitation path, assigned to the industry, is, also, evident by the citations found in the patents, 68 % of which come from public institutions (Czarnitzki et al., 2012).

Still in its infancy, much of the work in the sector involves R&D and it is, thus, crucial that the players involved work together efficiently. Knowledge transfer between universities and firms has become increasingly institutionalised as universities look for novel, more insightful, ways to enhance their economic and societal value through new technology spin-offs or start-ups, and firms are eager to secure future technologies (Colombo et al., 2014). Clearly, this academia-to-industry transition does not follow the, already challenged by many scientists (Balconi et al., 2010), 'linear model', where the university produces science, a part of which is then shaped into a marketed technology by the industry, but it is presented as an iterative, back and forth, process that may possibly manage to redefine research boundaries and university-industry linkages. The understanding of the mechanisms underlying this transition is considered a key parameter in determining the R&D value cycle of nano-enabled biomedical devices (Gurney et al., 2014). This is of particular significance to Europe that wants to improve the social rate of return from academic research given that the public funding level is competitive but the industry is lagging behind (Hullmann, 2006).

This paper uses biosensors as an exemplar of nano-enabled biomedical devices to study the dynamic structure of the innovation system, in an attempt to frame it by considering (i) its scientific basis, towards (but not through) its commercial applications (within-academy R&D), and (ii) the factors intrinsic to the technology itself (technology barriers) that could ultimately determine its rate of commercialization (R&D transfer from academy to industry). The work presented draws from the huge scientific and technical literature on the subject in order to track and evaluate the various developmental paths emerged in the academic environment (Siontorou and Batzias, 2013). Biosensors utilize nano-sized biological molecules or systems for the detection of clinical parameters. Preceding the nanotechnology era, they represent the early attempt to engineer nanomaterials for producing lab-on-chips, artificial sensing organs and implantable diabetes regulators. Three cases are presented and discussed: glucose self-monitoring, where the early industry interception ensured rapid commercialization, ion selective field effect transistors, where the iterative academy-to-industry transition is evident, and bilayer lipid membrane platforms, where the transition to industry is limited.

2. Building the biosensor innovation hub – A retrospective analysis

The pioneering work of Leland C. Clark, Jr. in 1960s that transformed an oxygen probe into a glucose meter, paved the way for the evolution of biosensor revolution. Markedly, a strong and effective university-industry alliance has been formed at the 1980's (Siontorou and Batzias, 2013), almost entirely on glucose meters and mostly in the USA, aiming at solving rapidly scientific and technical problems and at building capabilities in line with customers' requirements (Figure 1). Gradually distancing itself from the university science-base, the industry established a high competition arena at early 1990s and four R&D strategies to deal with the challenges and opportunities of diabetic management (inset to Figure 1): (i) intensifying the pull-basis towards the performance improvements, (ii) ascending the trajectory of the push-basis towards higher levels of efficacy, (iii) aligning with the needs of end customers, and (iv) increasing the market share with less costly formats and processes. When the marketed technologies became comparable in most critical aspects, new challenges (e.g., neonatal screening, non-invasive monitoring, etc.), urged the industry to look into the science push-pool for solutions and renew the university-industry link (note the increase in the number of university-industry joint papers/patents after 2000 in Figure 1).

On the other hand, the academic community realized the innovation as yet another advancement of the already well-established chemical sensor format: using the same instrumentation and experimental design, the chemical reaction was replaced by a biochemical one. The drive of the innovation system was indisputably the opportunity to exploit natural chemoreception. Diverse patterns of systems of innovation emerged as an outcome of mutual interaction of academic heritage resulting in an elaborate lattice-like structure of relations that supported clustering (Siontorou and Batzias, 2010). The between-clusters collaboration promoted largely the concept of biosensor applicability, especially at the advent of nanotechnology. Applicability was implicitly associated with marketability to enhance the R&D value (Fleischer et al., 2008). Research trends in biosensor design and fabrication have been shifted from modifying sensing surfaces towards the engineering of nanobiomaterials (Fonseca et al., 2014). The impact of nanotechnology is, also, evident in transduction schemes and integration strategies which, in turn, caught anew the interest of industry. Knowledge production followed a strong problem solving strategy, mostly divided in five optimization aspects (Figure 2): (i) performance, (ii) functionalization, (iii)

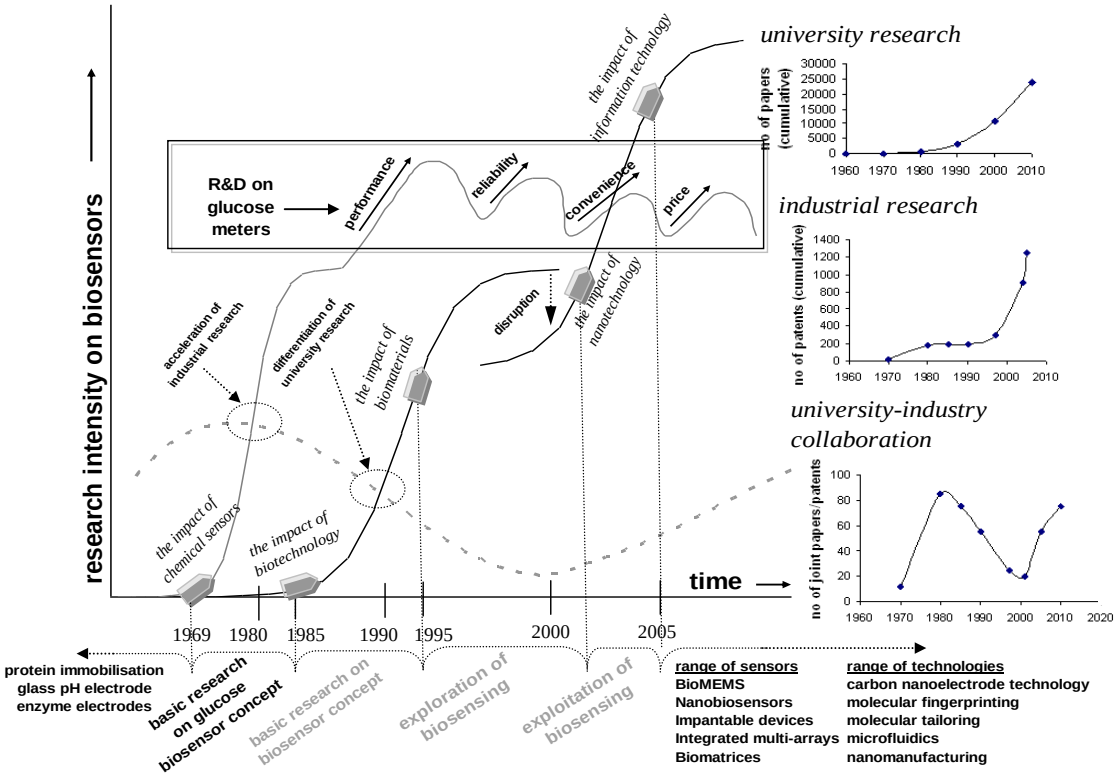

Figure 1: The glucose sensor R&D value cycle: (a) the socio-technical perspective (gray continuous line) drawn by the industry (via a cost reduction trajectory) as depicted with the inset), (b) the scientific perspective (black continuous line) drawn by the academic research. The disruption that occurred around 2000 signifies the accommodation of nanotechnology-based design and production that not only re-boosted biosensing (from both, scope and applicability) but also revived the university-industry collaboration (dashed gray line)

specificity, (iv) compactness, and (v) high throughput fabrication. Notwithstanding, many issues are still pending enabling a strong academic focus and a high rate of publications.

3. The university-to-industry transition– Analysis of the absorptive capacity

Ion selective field effect transistors (ISFETs) have been a very popular biosensor research field for both, the industry and the academy, since (i) their extended use in chemical sensing provided a well-established scientific and technical background at a high degree of technology exploitation that most biosensor groups familiarized with easily, and (ii) this technology represented, at that time, the only format available for clinical diagnostic and portable environmental device applications. Instability or drift was soon recognised as a main drawback prohibiting their commercialization (Bergveld, 2003). The small dimensions of ISFETs demanded strictly controlled fabrication and extreme accuracy in handling for yielding reliable devices. The process of photolithography presented many parameters, most of which could only be empirically estimated or indirectly approximated, e.g., the dielectric constant, the geometric sensitivity parameter, the gate oxide thickness or the diffusion coefficient. That gave rise to many problems, roughly translated to sensor drift (Bergveld, 2003): non-homogeneous doping distribution could not permit the stabilization of the bulk potential and the correct estimation of the ideal voltage threshold; the presence of excessive carriers could alter the expected electrical characteristics (conductivity), resulting in fallacious values of threshold voltage; excess diffusion of the oxidizing gas induced stacking faults altering the dielectric properties of the film.

ISFET technology fostered within the university absorbed rapidly the solutions provided by nanotechnology, shifting to nanopatterning to gain better control of the process and provide the industry

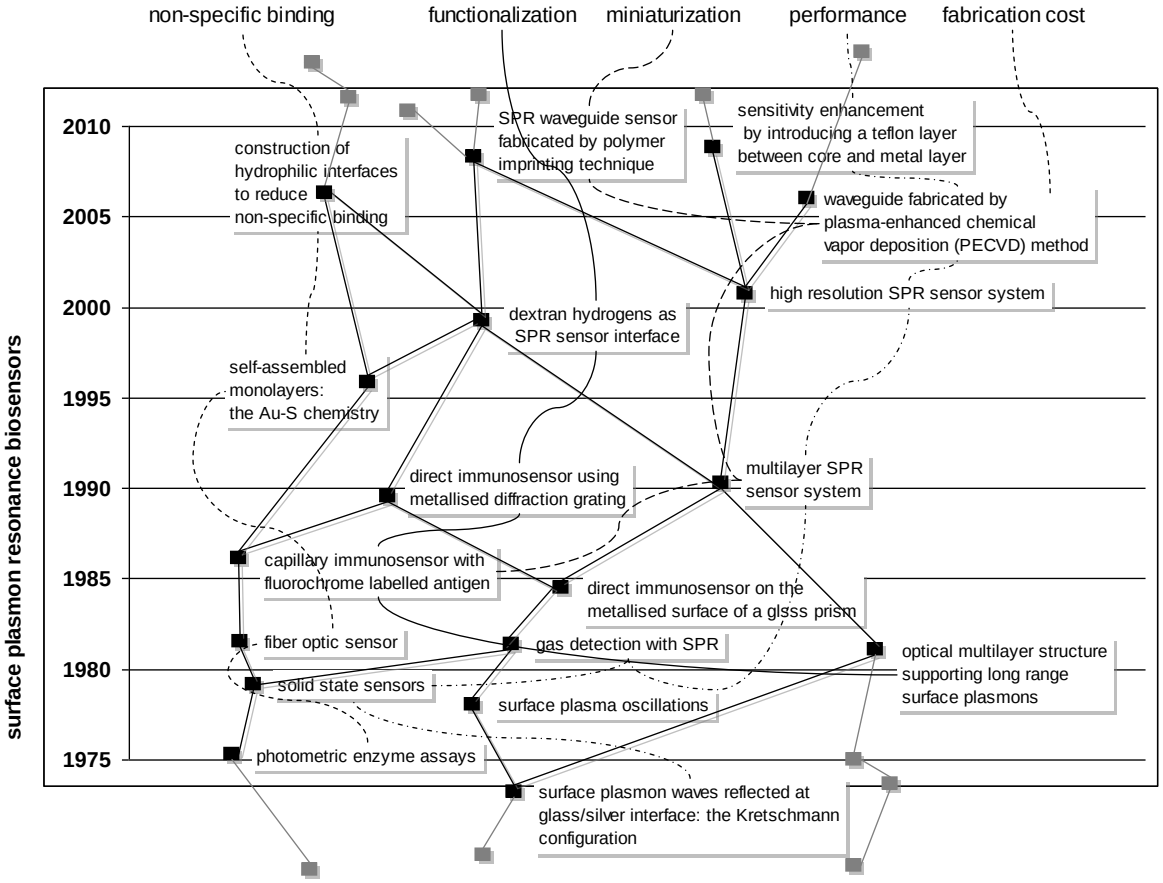

Figure 2: Excerpt from the scientific and technology map of university-derived biosensors, referring to one class that has been influenced heavily from technology or knowledge gaps, i..e, surface plasmon resonance biosensors. Straight lines indicate the linear advancement from one level to the next; in each class the dashed trails indicate the paths followed, each dealing with solving a significant drawback

with a customised and easy to scale-up set-up. Lithography-based patterning in nano-scale reveals, nowadays, mostly a strong dependence of apparatus cost with downsizing. In anticipation of broad-applicability of ISFETS, industry promotes research efforts towards new materials, like ruthenium oxides, that could not be handled before, film electrode patterning and integration.

4. Technology barriers – Analysis of the transformative capacity

Lipid membranes are two-dimensional fluid nano-structures where two, preferably, lipid layers are held together by non-covalent hydrophobic interactions of amphipathic molecules. The films have a thickness of about 5 nm, varying with the lipid tail length. For analytical applications, various biological moieties are incorporated into the membranes to add functionality (Venkatanarayanan and Spain, 2014). Although sensor's sensitivity and selectivity towards a given analyte are endowed by the biological moiety, speed of response and reversibility rests on the lipid film (Batzias and Siontorou, 2005): the thinner the film, the less time will take for analytes or products to diffuse and thereby, the lesser the time of response and the easier the reversibility.

The developmental paths drawn by the academy focus mostly on stability and manufacturability to ensure marketability (Figure 3). Nanofabrication was thought of as a suitable solution to both problems, presenting the rivalry of altering lipid composition versus supporting membranes on solid or porus substrates. The latter seems to gain momentum as these platforms have the competitive advantage of preserving the outstanding nature-derived sensitivity, although the supporting chemistry and engineering may hamper transduction (Kiessling et al., 2009). Nonetheless, the general conditions for stability of a system, particularly a membranous one, are given by the thermodynamics: the membrane is stable when its free energy has a minimum value in the space of the independent thermodynamic variables (Almeida, 2009). This means that any infinitesimal change of the independent parameters should lead to an increase of the

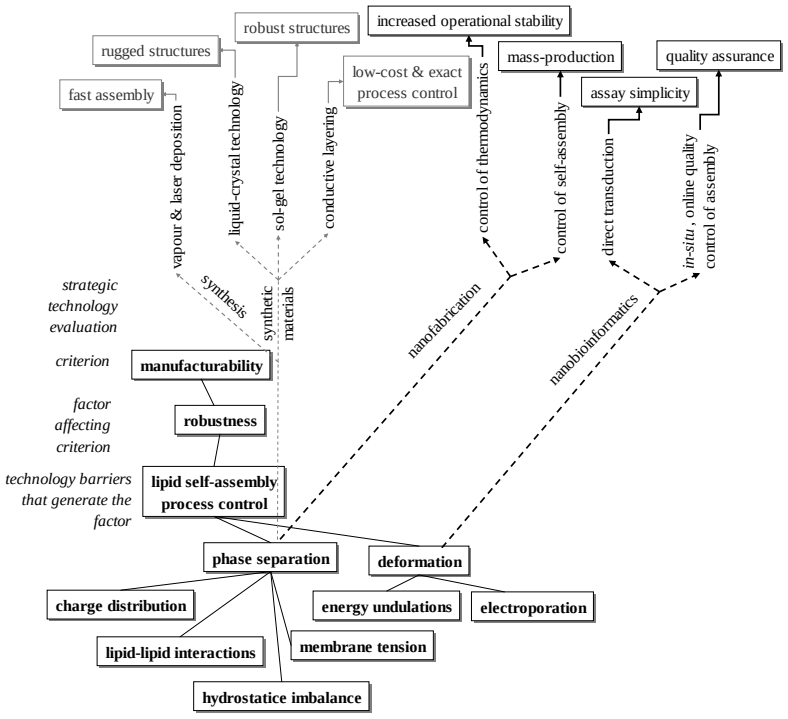

Figure 3: The strategic technology evaluation of membrane biosensors, related to manufacturability. The technology barriers shown relate manufacturability to stability; the right-part progress based on nanotechnology absorption is less probable to succeed its goals or proceed the left-part (bold lines) development scenarios based on using nano-science to widen the scientific base

free energy of the system. However, in many cases, as during protein shifting or flip-flop, the membrane can be unstable with respect to some of the thermodynamic parameters, but the rate of change of the membrane state is so small that during the characteristic time-scale of the experiment, this membrane behaves as stable; that is the case of 'meta-stable' membranes. Evidently, membrane instability is directly linked to both, manufacturability and functionality, with opposite effects, a tradeoff that it is not easily tackled with without advanced knowledge of the biological mechanisms down to molecular level, which is, currently, not available. It thus follows that the R&D value cycle should include the revisiting of basic science paths and nanotechnology should rather provide the means to study natural chemoreception mechanisms than to manipulate engineered biological systems.

5. Concluding Remarks

The R&D value cycle of nano-enabled devices has been frequently seen through the market base, applying the tools, methods and expertise developed for the biotechnology era. Nanoscience, however, has emerged quite differently, offering many advancements that may fit many disciplines and revolutionize many sectors. This versatility involves a constant interplay between knowledge exploration and exploitation that only academia can conduct and shape into numerous developmental paths, not only due to its traditional role of knowledge creator but also due to the high cost of research. Thus, if underestimation of the innovative potential or capacity of academic output is to be avoided, the value chain should be considered not from the point of industry interception but from the point of knowledge inception. This work indicated that in any attempt to analyse the R&D value cycle of an academic innovation system one should consider and evaluate that: (i) University research is mostly self-regulated, dynamically oriented towards various strategic targets until knowledge accumulation adequately supports certain research paths to become dominant (pull-basis), as shown in the case of ISFET technology. (ii) The strategic priorities of academic innovation may not be understood or clarified when the frame is structured or when the clusters are defining their scope, inasmuch as academia purports to enhance knowledge creation/exploration. This may align well with the pull-basis, as shown from the successful case of glucose sensing, or not, as in the case of the membrane nano-platforms, preserving, though, enough degrees of freedom to generate disruptive concepts.

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References

Allarakhia, M., Walsh, S., 2011, Managing knowledge assets under conditions of radical change: the case of the pharmaceutical industry, Technovation 31, 105–117.

Almeida P.F.F., 2009, Thermodynamics of lipid interactions in complex bilayers, Biochim. Biophys. Acta – Biomembranes 1788, 72-85.

Balconi M., Brusoni S., Orsenigo L., 2010, In defence of the linear model, Res. Policy 39,1-13.

Batzias F.A., Siontorou C.G., 2005, Investigating the causes of biosensor SNR decrease by means of fault tree analysis, IEEE T. Instrum. Meas. 54, 1395-1406.

Bergveld P., 2003, Thirty years of ISFETOLOGY. What happened in the past 30 years and what may happen in the next 30 years, Sens. Actuat. B.-Chem. 88, 1-20.

Bishop K., D'Este P., Neely A., 2011, Gaining from interactions with universities: Multiple methods for nurturing absorptive capacity, Res. Policy 40, 30-40.

Colombo S., Nazir S., Gallace A., Manca D., 2014, Experiment-based decision making in complex systems, Chemical Engineering Transactions, 36, 85-90, DOI:10.3303/CET1436015

Czarnitzki D., Hussinger K., Schneider C., 2012, The nexus between science and industry: evidence from faculty inventions, J. Tech. Transf. 37, 755-776.

Delgado G.C., 2010, Economics and governance of nanomaterials: potential and risks, Technol. Soc. 32, 137-144.

Fleischer T., Decker M., Fiedeler U., 2008, Assessing emerging technologies—Methodological challenges and the case of nanotechnologies, Technol. Forecast Soc. 72, 1112-1121.

Fonseca M.G., Batista L.N., Silva V.F., Soares T.C., Alves Romeiro G., 2014, Carbon nano compound from seeds: methodology to obtain a high added value product, Chemical Engineering Transactions, 37, 649-654, DOI:10.3303/CET1437109.

Gurney T., Horlings E., van den Besselaar P., Sumikura K., Schoen A., Laurens P., Pardo D., 2014, Analysing knowledge capture mechanisms: Methods and a stylised bioventure case, J. Informetr. 8, 259-272.

Hullmann A., 2006, The economic development of nanotechnology - An indicators based analysis, European Commission, DG Research, Unit "Nano S&T - Convergent Science and Technologies", <cordis.europa.eu./nanotechnology>, accessed 31.01.2014.

Kiessling V., Wan C., Tamm L.K., 2009, Domain coupling in asymmetric lipid bilayers, Biochim. Biophys. Acta – Biomembranes 1788, 64-71.

Kostoff R.N., Murday J.S., Lau C.G.Y., Tolles W.M., 2005, The seminal literature of nanotechnology research, J. Nanopart. Res. 8, 193-213.

Nicola S., Leon S., Nayak S., Mentzer R., Mannan M.S., 2013, Revisiting age old corrosion problems with modern tools and techniques, Chemical Engineering Transactions, 31, 673-678, DOI:10.3303/CET1331113.

Sapsalis E., van Pottelsberghe de la Potterie B., Navon R., 2006, Academic versus industry patenting: an in-depth analysis of what determines patent value, Res. Policy 35, 1631-1645.

Siontorou C.G., Batzias F.A., 2010, Innovation in biotechnology: moving from academic research to product development – The case of biosensors, Crit. Rev. Biotechnol. 30, 79-98.

Siontorou C.G., Batzias F.A., 2013, A methodological combined framework for roadmapping biosensor research: a fault tree analysis approach within a strategic technology evaluation frame, Crit. Rev. Biotechnol. 34, 31-55.